Nov 17, 2021 - Vol 4, Issue 9

ARCADIA

Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke

Next Webinar: Nov. 23 2021 AT 2 PM ET/1 PM CT/12 MT/11 AM PT

MILESTONES

Randomized = 756 **Consents = 2852**

October Randomizations = 14 **October Consents = 61**

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

80 Sites with 100% Retention Rate

Central Pharmacy Holiday Hours

Thanksgiving week: 11/23/2021 will be last day of shipping study drug kits to sites until Monday 11/29/2021.

Christmas week: 12/22/2021 will be last day of shipping study drug kits to sites until Monday 12/27/2021.

New Year's week: 12/29/2021 will be last day of shipping study drug kits to sites until Monday 1/3/2022.

CALM Lab Holiday Hours

Thanksgiving week: You can ship blood samples Monday & Tuesday (11/22/21-11/23/21) The usual shipping schedule resumes Monday (11/29/2021).

Christmas week: You can ship blood samples Monday-Wednesday (12/20/21 to 12/22/21) The usual shipping schedule resumes Monday (12/27/2021)

New Year's week: You can ship blood samples Monday-Wednesday (12/27/21 to 12/29/21) The usual shipping schedule resumes Monday (1/3/2022)

If you obtain specimens and can't ship due to the holiday hours, please process the specimens per the CALM core lab manual to ship when the lab is open.

SPOTLIGHT ON SITES

October Top Consenting Sites

Hospital of the University of Pennsylvania - 4

UPMC Presbyterian Hospital- 3

Oregon Health & Science University Hospital - 3

Columbia University Medical Center - 3

McLaren Macomb - 3

Yale New Haven Hospital - 3

October Top Randomizing Sites

2 randomizations each!

**Oregon Health & Science University Hospital
Portland, Oregon**

**Methodist University Hospital
Memphis, Tennessee**

Welcome Aboard!

No new sites were released to enroll in October but 15 new sites are in start-up with some close to release to enroll!

We are so thankful for our sites and wish you a very Happy Thanksgiving!

Science Corner—Update from the American Heart Association Scientific Sessions 2021

Atrial fibrillation (AF)—and its neurological consequences, including cognitive decline and dementia—were a hot topic at this year's Scientific Sessions. Three studies may be of particular interest to ARCADIA investigators

GIRAF (presented by Bruno Caramelli, Sao Paolo, Brazil: a Brazilian cardiologist, but whose brother is a neurologist).
GIRAF was a multicenter, randomized, controlled but unblinded trial of dabigatran vs warfarin to prevent cognitive decline and dementia among patients with atrial fibrillation. The rationale for the trial is that cognitive decline and dementia are common in patients with AF and may be due to both ischemic events and cerebral microbleeds; thus, newer anticoagulants with a more favorable profile in terms of reducing ischemia without as much increase in bleeding risk can be hypothesized to reduce cognitive adverse effects compared to standard anticoagulants like warfarin. The study was performed at 6 centers in Brazil. The investigators enrolled patients ≥70 years old, with history of AF or atrial flutter, and CHADS2-VASc score >1. They excluded patients with dementia or previous stroke. Patients were randomly assigned 1:1 to dabigatran (110 or 150 mg BID, depending on standard thresholds) vs warfarin (INR 2-3). The primary endpoint was cognitive impairment at 2 years, assessed by performance of a variety of cognitive tests including the Mini-Mental State Exam (MMSE), Montreal Cognitive Assessment (MOCA), and a comprehensive neuropsychological test battery.

Bottom line: No major differences in outcomes at 2 years, although there was evidence that patients on warfarin had less decline on the MOCA than patients on dabigatran. Results were not consistent across other tests, however. There were several limitations to the study, including: small sample size, short duration of follow-up, unblinded design, study limited to those without history of stroke, lack of details about stroke during follow up, no dementia outcomes presented. Further details will be interesting to see whether there were differences by subgroups.

ASCEND (presented by Jane Armitage, Oxford)
ASCEND was a UK-based study that tested the effect of aspirin 100 mg daily vs placebo in diabetic patients. In this secondary analysis, the investigators presented results on the effect of aspirin on dementia. The rationale for the study is that daily aspirin could be associated with both a reduction in vascular events and also an increased risk of brain bleeding, including cerebral microbleeds. Aspirin may also have anti-inflammatory and anti-amyloid effects that could be of benefit against cognitive decline and dementia. Thus aspirin could have opposing beneficial and adverse effects on cognition. The investigators hypothesized that aspirin 100 mg daily would reduce dementia. They conducted a randomized, controlled, blinded trial in the UK. Eligible patients were ≥40 years old, diabetic and free of prior cardiovascular disease. They enrolled 15,480 patients, who were followed a mean of 7.4 years in the trial and an additional 1.8 years after the trial. Outcomes of dementia were assessed using medical record linkage.
Bottom line: non-fatal serious vascular events and major bleeding were both associated with an increased risk of dementia (broadly defined); aspirin, compared to placebo, was associated with a potential modest impact on reduced risk of dementia, but the result was not statistically significant (rate ratio 0.91, 95%CI 0.81-1.02). Despite several limitations (study limited to patients with diabetes, dementia a secondary outcome for which medical records were used to make the diagnosis, and a single dose of aspirin tested), the results suggest a potential benefit for aspirin though more research is needed. It is reassuring, however, to see cognitive outcomes being addressed in this trial.

Fitbit Heart Study (presented by Steve Lubitz, MGH)
The rationale for this study, like for the Apple watch study published in NEJM a couple of years ago, is the idea that easy-to-use consumer-directed technologies (like wearable devices) could be used to detect a high-risk condition like AF and thereby prevent stroke. Fitbits use optical plethysmography (PPG), which can be used to detect pulse irregularity, which may indicate AF, but needs to be confirmed with a more formal test for AF. The investigators of this study hypothesized that the detection of AF on a Fitbit fitness tracker has a high positive predictive value for AF detected on subsequent patch monitor worn for a week. They performed a parallel group, randomized, controlled, unblinded trial in US, enrolling an incredible 455,699 people (during the pandemic!) over age 22. Participants were randomized to notification of an irregular heart rhythm detection (IHRD) versus none. Among those in the notification group, 4728 had irregular heart rhythm detected, of whom 1671 went in for a confirmation visit, and 1162 returned ECG patch monitors. Ultimately 340 patients had AF during the subsequent monitoring, or 32% of those with irregular heart rhythm detected. The positive predictive value for AF was 98%; median AF burden was 7%, and the median duration of episodes of AF was 7 hours. A small number of participants had clinical changes made based on these findings, more than in the group randomized to get heart rhythm detection notifications, although clinical outcome analysis is not yet finished.
Bottom line: Consumer directed wearables have good PPV for detection of AF, and may change management in a small number of patients. Limitations of the study were that it required 30 minutes of irregular heart rhythm to detect (and we know episodes may be shorter than this and still clinically relevant and causative of stroke); no patch monitors in those without IHRD alert; uncertainty regarding clinical benefits and cost implications; and low rates of engagement after IHRD detection (only 35% sought out further evaluation). Further research will be needed to see how these devices can be fully utilized in clinical care.

PROJECT MANAGER STUDY REMINDERS

- Check the ARCADIA Toolbox in WebDCU for valuable information such as the core lab manuals, protocol, tools for subjects and many more documents to help you enroll patients.
- If your subject is tiring of the study and wants to stop, please offer the following options, if not on study drug, before ending their participation:
  - Less frequent visit options such as every 6 months. Conduct an EMR visit in between
  - Offer to only check in via phone call
  - Ask if they can be followed via EMR only
- All con meds must be reviewed at every visit to avoid prohibited medications.
- All regulatory documents for a new team member must be uploaded & approved before that person can work on the ARCADIA study.
- Remind your subjects not to take study drug from bottles that have already been checked for study drug adherence.
- If you received an email stating your eConsent has been built, you need to apply for a REDCap user ID using the link sent in the email. The eConsent cannot be sent to you until user rights are assigned.
- Out of window visits are still being tracked. Please make every effort to conduct your subject visits within window. If you are unable to contact your subject, complete an EMR check within window and update the visit if the subject returns the call.

FAQ

Question: The patient seems to have all of the inclusion/exclusion criteria, however they have CADASIL. Does CADASIL lend itself to the stroke not being ESUS, and the patient not being eligible?

Answer: If your treating team & site PI think this stroke was due to the CADASIL (Cerebral Autosomal Dominant Arteriopathy with Sub-cortical Infarcts and Leukoencephalopathy), then this patient is not ESUS as there is a known cause for their current stroke. CADASIL is a cause of stroke, so this patient most likely would not qualify.

Also, the types of strokes that occur in CADASIL are small vessel, so it is would seem unlikely that the stroke is a ESUS-type stroke, which by definition are not small vessel; ESUS are generally superficial cortical infarcts.

Of course, it is possible that the patient has a separate ESUS stroke on top of their CADASIL type strokes, but that seems unlikely.

WebDCU Database Freeze

ARCADIA will have a database freeze on November 29.

Please make sure to address any outstanding queries and missing data before that date.

Calendar of Events

November 18 - SC Open Conference Call

November 23 - Monthly Webinar

November 11 - Veterans Day

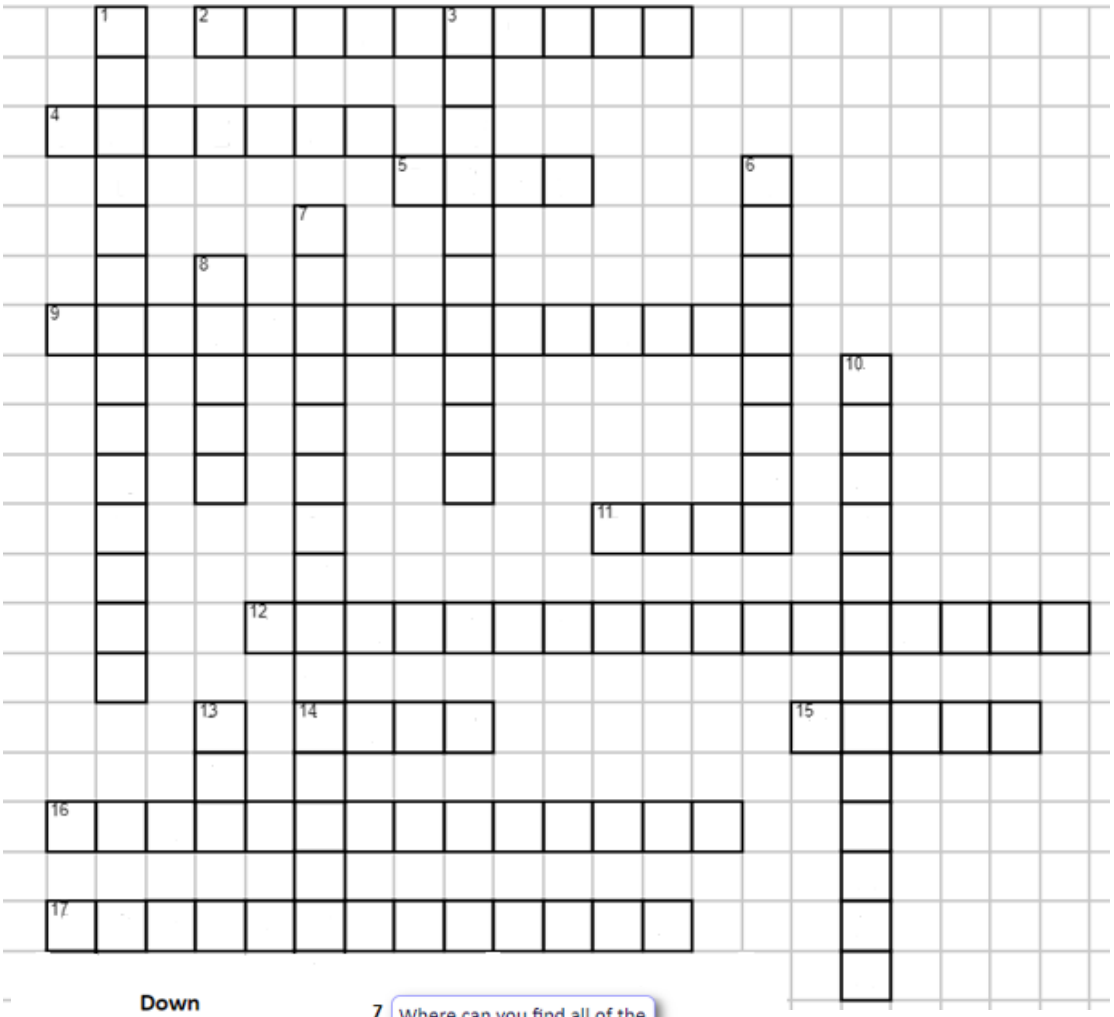
November 25 - Thanksgiving

November 29 - Database Freeze

December 2 - SC Open Conference Call

December 16 - SC Open Conference Call

Just For Fun!



Across

2 You call (833) 427-2234 for what emergency reason?

4 An event of any untoward medical occurrence or worsening of a current medical condition.

5 What group of independent people monitor the safety of the study?

9 What is the primary endpoint of the study? (2 words)

11 How many days do you have to add visit data into the CRFs?

12 Subjects must meet at least one of these criteria to be able to be randomized. (2 words)

14 Type of stroke the patient must have for inclusion.

15 What disease process is assessed at every follow up visit?

Down

1 What assessment scale must be less than or equal to 4 for inclusion? (2 words)

3 Where can you find the ARCADIA contact list?

6 What visit includes the consent of the patient?

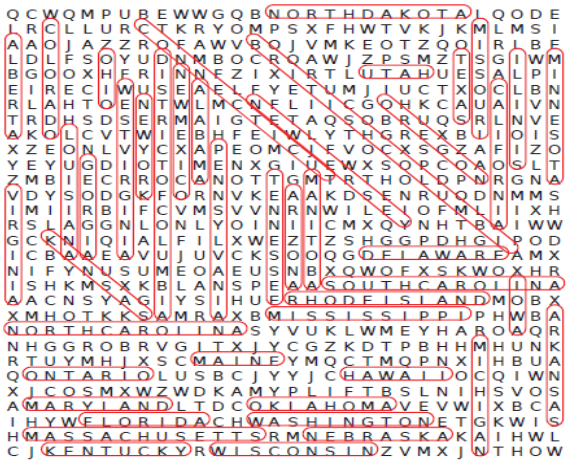
7 Where can you find all of the webinar recording? (2 words)

8 What shows up as "pink" on a subject visit?

10 What tab in WebDCU do you find if your subject meets randomization criteria? (2 words)

13 Brain imaging for inclusion can include CT or ?

October Word Search Solution



Alabama	Kentucky	North Dakota
Alberta	Louisiana	Ohio
Arizona	Maine	Oklahoma
Arkansas	Manitoba	Ontario
California	Maryland	Oregon
Colorado	Massachusetts	Pennsylvania
Connecticut	Michigan	Rhode Island
Delaware	Minnesota	South Carolina
District of Columbia	Mississippi	Tennessee
Florida	Missouri	Virginia
Georgie	Nebraska	Washington
Hawaii	New Jersey	West Virginia
Illinois	New Mexico	Wisconsin
Iowa	New York	
Kansas	North Carolina	

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

The Greek Festival of Thesmophoria—Giving Thanks

In ancient Greece, a festival used to be held in about 50 cities or villages, to honor the goddess who taught mankind to tend the soil. In Athens, only the women met to celebrate.

Thesmophoria, Θεσμοφόρια, in ancient Greek, honors the goddess Demeter and her daughter Persephone. The festival was born of a mother's love for her daughter as Demeter lay mourning Persephone's captivity in the Underworld. Demeter's mourning period coincided with fall, when the Earth sheds its greenery in anticipation for the cold months ahead.

Meanwhile, her mother Demeter despaired and searched for her daughter, refusing to let the land blossom until her return. Zeus knowing Persephone had tasted the pomegranate fruit relented--but with conditions. Agreeing to let Persephone return to her mother, he decreed that she spend part of her time each year in the Underworld with her husband Hades. Thus, Persephone's innocent taste led to the creation of the seasons. Sadly, while Persephone languishes in the Underworld, so too does Earth languish in winter. Her return heralds spring's return and Earth's rebirth.

Scholars are uncertain when the festivals began, however, they suspect the festival dates back to the 11th century BCE and was held during a month known as *Pyanopsion* (*Puanepsion*), in the lunisolar calendar of the Athenians. Since our calendar is solar, the month doesn't exactly match, but *Pyanopsion* would be, more or less, October into November, the same months as the Canadian and U.S. Thanksgivings. In ancient Greece, this was the time of the fall planting of crops like barley and winter wheat.

On the first festival day, Athenian high born women went in procession to the deme of Halimus, on the promontory of Colias in Athens, followed by taunts and jests of men. Three nights of celebration followed, during which the women worshiped Demeter and her daughter. After three days passed, they returned to Athens

Though details surrounding ritual sacrifice are somewhat vague, scholars generally agree that pigs were sacrificed and held in pits called Megara to decompose. The women, having spent days in a state of ritual purity, subsequently retrieved the remains. As well, they baked phallic and snake shaped cakes to place together with the remains on Demeter's alter. Though the details are murky, the intention seems clear - appeal to Demeter's generosity, sow the seeds with pig fertilizer and pray for fertility in both harvest and family.

Thanks to the following website for the information: https://www.tolmee.com/blogs/news/thesmophoria-the-ancient-greek-festival-of-giving-thanks