October 22, 2020 - Vol 3 Issue 10

ARCADIA

Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke

Webinar Tuesday 10/27 at 2p EST/1p CT/12 MT/11p PT
Next Month: November 24 AT 2 PM ET/1 PM CT/12 MT/11 PM PT

MILESTONES

Randomized - 523 Sept. Randomizations = 25 Consents—1972 Sept. Consents = 63

SPOTLIGHT ON SITES

September Top Randomizing Sites

UPMC Presbyterian Hospital - Pittsburgh
3 randomizations

United Hospital—St. Paul
2 randomizations

September Top Consenting Sites

Memorial Hermann - 4 consents

Yale, Emory & UPMC Presbyterian
each with 3 consents

Welcome Aboard - September New Sites

Akron General Medical Center, Akron, OH.; West LA VA Medical Center, Los Angeles, CA.; Bon Secours St. Mary's Hospital, Richmond, VA

AE Reporting Tip - Assembling the Event Packet—Form 104 (Q17)

Providing relevant medical records in support of an adverse event (AE) is an important part of reporting. Accurate and complete information is needed for the Medical Safety Monitor to determine expectedness, seriousness, and the relationship of the AE to the study treatment. It is also necessary for the adjudicators to complete their reviews.

But more does not equal better! Medical records often contain information that is repetitive or specific to the institution. Sorting through excessive information makes it difficult to find the facts related to the AE.

Use the ARCADIA Checklist for Preparing Event Packets located in Project Documents in WebDCU as a guide for what documents to include based on the specific type of event.

When the subject is hospitalized, documentation of the date of onset, presenting symptoms, treatment and any complications are needed. Usually the admission notes, relevant laboratory tests and imaging reports along with the discharge summary are sufficient. For subjects who have complicated events or multi-system issues, consultations should be included.

For events treated as an outpatient (such as AF) the MD note diagnosing the event and rhythm strips/ECG demonstrating the AF is sufficient documentation.

For most AEs daily physician progress notes and nursing notes are not needed.

Please remove subject discharge instructions, blank pages, pages that contain physician orders, descriptions of tests, lists of providers, descriptions of the type of imaging equipment used, calibration information or hospital specific procedures.

If additional information is added to an already uploaded packet, the entire packet must be re-uploaded.

Science Corner

COMPASS-MIND fails to demonstrate benefit of anticoagulation on cognition and covert infarcts

COMPASS-MIND (Cardiovascular Outcomes for People Using Anticoagulation Strategies MRI and Neurocognitive Deterioration) published results in the October 2020 issue of *Stroke.*[1] This was a substudy of COMPASS, which compared rivaroxaban with and without aspirin, and was stopped early because of the significant reduction of the composite endpoint of vascular death, myocardial infarction and stroke with combined therapy. COMPASS MIND (also referred to as COMPASS MRI) sought to determine whether these antithrombic treatment arms had a differential impact on incident covert brain infarcts.

The COMPASS trial randomized 18,278 individuals, of whom 1445 participated in the MIND substudy and underwent baseline MRI and neurocognitive testing. The patient population included those with a history of CAD (90%), peripheral artery disease (26%), carotid stenosis ($\geq$50%) or previous revascularization (7.6%), and TIA or stroke (6%). Mean follow-up was 2.0 $\pm$ 0.7 yrs. Incident covert infarcts occurred in 3.8% of individuals. There was no difference in infarcts or neurocognitive test results across treatment groups.

Comment: At first blush this ancillary study to COMPASS may seem to imply that we are unlikely to find an effect of antithrombotic therapy on covert infarcts or cognition in our own ancillary study, ARCADIA-CSI. Several differences between COMPASS-MIND and ARCADIA-CSI should be noted, however. First, COMPASS included a heterogeneous patient population, with only 6.3% with symptomatic stroke or TIA. Second, ARCADIA-CSI focuses on patients with atrial cardiopathy, who are thus expected to have a higher likelihood for silent infarction. Third, our planned follow-up will be as long as four years compared with only two in COMPASS. Finally, COMPASS used the MoCA and the Digit Symbol Substitution Test, whereas our battery is longer and more sensitive. The impact of anticoagulation on cognition in patients with atrial cardiopathy remains an open question that ARCADIA-CSI will address.

Reference:

1. Sharma M, Hart RG, Smith EE, et al. Rivaroxaban for Prevention of Covert Brain Infarcts and Cognitive Decline: The COMPASS MRI Substudy. *Stroke.* 2020;51:2901-2909.

Thanks to ARCADIA-CSI Co-PI Ron Lazar, PhD for this summary of COMPASS-MIND

FAQs

Question: 1 One of our ARCADIA patients had a breast biopsy that shows malignancy. I would like to request unblinding, and we may start her on anticoagulation. Can we keep her in the trial on study drug if it turns out that she was assigned to apixaban?

Answer: This case brings up several points. First, there is no evidence that patients with stroke who are found to have breast cancer should all be treated with anticoagulation. The decision to do so remains a clinical judgement call, but is not required. Second, patients will not be unblinded for non-emergent issues; in this case, knowing whether the patient is on apixaban or not would not change management. Third, once a patient is unblinded they do not continue study drug. Finally, the occurrence of cancer in a patient being followed in ARCADIA constitutes an adverse even of special interest, and this must be reported as an AE, even if the patient is not hospitalized and this is not an SAE.

Question: 2 Can subjects be on DAPT (Plavix + aspirin) until the day before they are randomized?

Answer: Yes a patient can be on DAPT prior to randomization as long as there is no aspirin or Plavix being taken after randomization.

Updates/Reminders/Tips

- No study procedures can be completed until you have conducted the informed consent process with the potential participant and they have signed the Informed Consent Document.
  - This includes the biobanking section whether or not they are participating.
- Do not prescreen a patient based on your institutional results for NTproBNP or Echocardiogram. All cardiopathy criteria are evaluated by ARCADIAs Core Labs.
- Please review all Inclusion/Exclusion criteria including your EMR before approaching the patient regarding participation.. This means checking all protocol required test results even if the physician says they're eligible as the tests may still be pending.
- Please engage your colleagues, not only neurology but cardiology and primary care, so that they have exposure to the study and can collaborate with you on your participants' enrollment and also refer potential participants.
- Using a witness is required when consenting a non-English speaking patient. The witness cannot be part of the study team.
- When to closeout a subject:
  - Subjects who withdraw consent can be closed immediately but not before asking if we can follow via EMR if they aren't willing to just allow phone follow-up.
  - Subjects who acquire an SAE , if adjudicated that they have reached primary outcome, can be closed out 30 days after study drug discontinuation.
  - DO NOT closeout subjects who develop Afib, come off study drug or unblinded but did not have a primary outcome
- Review medications at every follow up visit to guarantee the subject is not taking prohibited medications.
- If you are unsure if a patient meets I/E criteria, use the ARCADIA email to get a quick response.

ARCADIA@ucmail.uc.edu

Top 10 Lessons learned from calls with sites that have had difficulty enrolling

1. Use the ARCADIA video to help explain the trial to patients: https://youtu.be/YIneZ4n-xXE
2. You can enroll patients with hemorrhagic conversion
3. You can enroll patients with PFO if they are not having PFO closed (or if they are having it closed, you can enroll them after they come off post-procedure antithrombotics)
4. Patients with CKD are eligible if their creatinine elevation does not remain elevated above 2.5
5. Have PI or sub-I explain study to patient
6. Don't give up on approaching potential participants just because they were discharged on Dual Antiplatelet Therapy (even if this will be temporary); patients can be enrolled after they stop DAPT, usually at about 30 days
7. Patients can be enrolled after completion of their participation in another trial (for example: MOST)
8. Have a strategy to deal with competing trials; once a subject has been enrolled in one clinical trial, they cannot be in another concurrent trial
9. Remind subjects that we can do consent, randomization and follow-up visits remotely so that they don't have to come back to the medical center every 3 months
10. Screen in real time and keep lists of potential subjects so that they can be approached as inpatients or after they have left the inpatient service. Review these so that there is a tracking system of accountability.

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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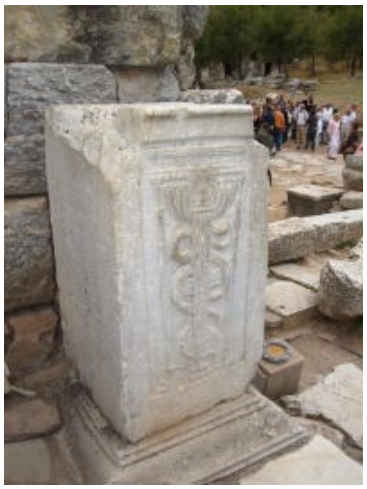
Greek Culture Corner

Ephesus and its medical legacy

Ephesus, on the western shores of modern day Turkey, remains an impressive site for the quality of its ancient remains. The city was founded by Greek colonists in the 10th century BC. A small city by our standards, its population numbered 150,000. It was known for the quality of its medicine and public health. There were temples that also functioned as hospitals, physicians trained in the teachings of Asclepius (featured in prior ARCADIA newsletters), and even public, communal toilets. By the Roman era, it was the site of medical schools. Ephesus produced at least two famous physicians. The first, Rufus of Ephesus, emphasized the importance of the history and of the physical examination. He also proposed an early diuretic: the application of poultices of grilled cicadas. The second was (the unfortunately named) Soranus, who wrote about obstetrical and gynecological topics, including peripartum infection, and provided the first account of infantile rickets. Architectural highlights also included the Temple of Diana, considered one of the seven wonders of the ancient world. Unfortunately an arsonist burned it down in 356 BC to make his name immortal; we won't contribute to fulfillment of that wish!

The ancient ruins of Ephesus



Hospital road sign