June 16, 2021 - Vol 4, Issue 4

ARCADIA

Atrial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke

Next Webinar: June 22, 2021 AT 2 PM ET/1 PM CT/12 MT/11 AM PT

MILESTONES

60% of Randomizations Completed!

Randomized - 670

April Randomizations = 24

May Randomizations = 19

Consents = 2514

April Consents = 76

May Consents = 67

146 Active Sites - U.S. = 140 & Canada = 6

Webinar Tuesday June 22nd

Please join us next Tuesday for our June webinar. The following topics will be discussed:

- Prohibited Medications Discussion
- 2nd Distribution of Site Performance Metrics
- Reconsenting Subjects
- Updated Visit Scheduler
- Updated Wallet Card with Medication Log
- OOW Visits

Please let us know if there are topics you would like to discuss.

ARCADIA SC Hero's

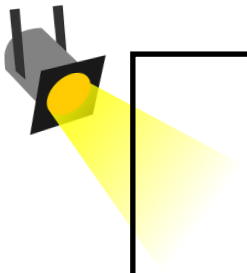
Teri McQuaid & Karen Rapp

UCSD Hillcrest & La Jolla Sites

Thanks to these two exceptional Study Coordinators for bringing a problem to the study team. Their diligence and extraordinary attention to detail helped identify a programming issue in the ECHO CRFs. In a matter of a couple of hours with help from the NDMC team the issue was identified and fixed.

We are so very grateful for your dedication to your subjects and the ARCADIA study!

SPOTLIGHT ON SITES



April Top Randomizing Site

UVA - 2 randomizations!

May Top Randomizing Site

Methodist Univ. Hospital - 2 randomizations!

April Top Consenting Site

UVA - 5 consents!

May Top Consenting Site

Methodist - 4 consents!

Sites with First Randomizations for April & May

UT Southwestern
Rancho Los Amigos
Strong Memorial
Hamilton General
Mount Sinai Beth Israel Brooklyn
Memorial Hermann The Woodlands
University of Alberta
Neurologic Research Center
Rush University

Welcome Aboard!

University of Alberta

Neurologic Research Center

The Queen's Medical Center

Vancouver General

London Health Sciences Center

Science Corner

The addition of aspirin to anticoagulation with direct-acting oral anticoagulants (DOACs) does not reduce ischemic events but increases risk of bleeding

In a registry-based cohort study at four anticoagulation clinics in Michigan (2015-2019), investigators assessed the risk of ischemic and hemorrhagic events among 3280 adults undergoing treatment with DOACs for atrial fibrillation or venous thromboembolism. The main exposure under study was the use of aspirin concomitant with DOAC therapy. There were 1107 (33.8%) patients without a clear indication for aspirin being treated with DOACs and aspirin. Patients were followed for a mean of 20.9 ± 19.0 months. In a propensity score–matched analysis, patients taking DOAC and ASA experienced more bleeding events compared with DOAC monotherapy (26.0 bleeds vs 31.6 bleeds per 100 patient years, P = .01). Thrombotic event rates were similar between the cohorts (2.5 events per 100 patient-years with DOAC vs 2.3 with DOAC and ASA; P = .80). Patients were also more often hospitalized while undergoing combination therapy (9.1 vs 6.5 admissions per 100 patient years, P = .02).

In summary:

- Nearly one-third of patients with AF / VTE treated with DOAC receive aspirin without indication.
- Compared with DOAC monotherapy, concurrent DOAC/aspirin use is associated with increased bleeding and hospitalizations but no benefits in reducing thrombosis.

Relevance to ARCADIA:

- Consider this balance of risks and benefits when discussing risks and benefits of ARCADIA, especially when patients' providers or family claim that patient should be on both DOAC and ASA, which is against ARCADIA protocol.

Reference: Schaefer JK et al. JAMA Intern Med.2021;181(6):817-824. PMID:33871544

ADAPTABLE trial shows no clear benefit of 325 mg aspirin over 81 mg

The ADAPTABLE trial used an open-label, pragmatic design to test the hypothesis that patients randomly assigned to aspirin 325 mg daily would have a lower risk of thrombotic events than those assigned to 81 mg daily. The primary effectiveness outcome was a composite of death from any cause and hospitalization for MI or stroke; the primary safety outcome was hospitalization for major bleeding. The investigators enrolled 15,076 patients who were then followed for a median of 26.2 months. Before randomization, 90% (n=13,537) were already taking aspirin (and 85% were taking 81 mg). Median weight of participants was 90 kg. In follow up, there was no significant difference in the occurrence of the primary outcome between groups, nor was there a difference in the occurrence of major bleeding (~0.6% in both groups). In a secondary analysis, there was more dose-switching among those on 325 mg daily, but those who stayed on 325 mg daily did have a modest benefit over those on 81 mg. Patient weight did not explain any lack of benefit in adjusted analyses. The study limitations included absence of blinding; a high rate of dose-switching; and the use of only virtual follow-up and identification of events through the medical records.

In summary:

- ASA 81 mg is adequate for secondary prevention compared to ASA 325 mg.

Relevance to ARCADIA

- ADAPTABLE validates our standard dose of 81 mg daily in ARCADIA
- ADAPTABLE provides no definite reason to use 325 mg daily, and this information can be shared with patients and caregivers or providers who inquire about use of a higher dose.

Reference: Jones WS, et al. Comparative Effectiveness of Aspirin Dosing in Cardiovascular Disease. N Engl J Med. 2021 May 15. PMID: 33999548.

Prohibited Medication Reminder—Letter to Sites sent on 6/17/2021

Dear ARCADIA Investigators and Coordinators:

We are writing today to remind you about how important it is to be certain that your ARCADIA patients take their study medications properly and that they do not take any prohibited antithrombotic agents. Recently two case examples came to our attention that have raised our concern for this situation.

Case 1: A previously randomized patient showed atrial fibrillation on loop recorder. Two days later, the patient's cardiac electrophysiologist started the patient on rivaroxaban (Xarelto). The local ARCADIA team was not informed of this by the cardiologist, and the patient continued both his study drug and rivaroxaban. When seen one week later by the study team, the patient informed them of this change in his medication, and he was instructed to stop his study medication immediately. There were no adverse consequences, such as bleeding, but the patient was at risk due to the potential to be on two anticoagulants simultaneously.

Possible solutions: One way this event could have been prevented is to be sure that treating physicians, including cardiologists, are aware of patients' participation in ARCADIA and what the medical treatments are. Sending letters or calling the other physicians could avoid this situation.

Case 2: Two months after her 3-month follow-up, a patient was contacted by phone to schedule her 6-month follow-up visit. Over the phone she reported that she had since visited another local hospital as an outpatient due to chest pain and atrial fibrillation was detected. The local cardiologist initiated apixaban (Eliquis) 2.5 mg BID, but she had continued study medication. The patient was instructed to stop taking study-related medication. Telephone visits continued per protocol, and the subject returned unused medication The study team promptly reported. There were no bleeding complications.

Possible solutions: It is also important to be certain that patients understand what the purpose of the medications in ARCADIA are, and that they understand why non-study antithrombotic agents are prohibited. Explain to patients that their safety is of paramount importance to us, and that prohibited medications on top of study drugs could increase their risk of bleeding. Use the talk-back method to be sure they understand what is being told to them.

As these events exemplify, it is extremely important to educate your patients, their family members, and their other treating physicians about their medications and what other medications to avoid. We have provided study wallet cards for this purpose. We will address this concern further on our upcoming June 22, 2021 2 PM ET ARCADIA webinar. We look forward to discussing additional thoughts and suggestions you may have as a way to avoid the potential adverse consequences of patients' being on prohibited antithrombotic agents.

Thank you for all you do to make ARCADIA a successful trial.

The ARCADIA Study Team

From our WebDCU Team

You must review the details of each of your subject's con meds at every visit. This is to be recorded in F288, the Concomitant Medication Log in the subject's CRF in WebDCU. Doing so helps prevent the subject from taking prohibited medications. It may also help identify and adverse events that may have occurred.

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 Horae & The Goddess of Summer

In Greek mythology, items of nature were usually personified in the form of a god or goddess. Among the most important of these beings were the Horae, a group of goddesses who ordered the seasons and natural time. As time progressed, the Greeks came to associate the Horae not only with natural phenomenon, but with justice and good order as well..

While the origins of the Horae differ according to source, most accounts put Zeus, the head of the Olympic Pantheon, as their father and Themis, the Titaness of justice, as their mother. Traditionally, the Horae appear in triads. The earliest Horae triad featured Thallo, Auxo, and Carpo, who looked after the natural order of the world. A later triad was composed of Eunomia, Dike, and Eirene. These three goddesses looked after justice and lawful order.

The Horae were particularly honored by farmers who planted and tended their crops in time with the rising and setting of the stars--measures of the passing seasons.

Auxo, was the goddess of summer and the increaser of plant growth. She was the protector of vegetation and plants, and growth and fertility.

Excerpts from theoi.com & greekboston.com

From the Antikensammlung Berlin Collection
The three Horae, Athenian red-figure kylix
C5th B.C.Auxo is pictured in the middle