ARTESIA

**CONDITION:** Sub-clinical atrial fibrillation (SCAF) detected by PPM, ICD, or ICM.

**PI:** JoEllyn Moore, MD

**SUB-I:** Manjunath Pai, MD

**CONTACT INFO:** Jacob Cohen, MS | jacob.cohen@allina.com | 612-863-4022

**DESCRIPTION:** Prospective, randomized, parallel group, double-blind trial to determine if the use of apixaban in patients with SCAF will reduce the incidence of stroke and systemic embolism compared to aspirin. The experimental part of being in this study is being randomized to either aspirin or apixaban.

**CRITERIA LIST/QUALIFICATIONS:**

**Inclusion:**
- Permanent pacemaker or defibrillator (with or without resynchronization) or insertable cardiac monitor capable of detecting SCAF
- At least one episode of device-detected SCAF ≥ 6 minutes in duration but no single episode > 24 hours in duration at any time prior to enrollment. Any atrial high rate episode with average > 175 beats/min will be considered as SCAF. No distinction will be made between atrial fibrillation and atrial flutter.
- Age ≥ 55 years
- Risk Factor(s) for Stroke:
  - Previous stroke, TIA or systemic arterial embolism OR Age at least 75 OR Age 65-74 with at least 2 other risk factors OR Age 55-64 with at least 3 other risk factors

**Exclusion:**
- Clinical atrial fibrillation documented by surface ECG (12 lead ECG, Telemetry, Holter) lasting ≥ 6 minutes, with or without clinical symptoms

**SPONSOR:** Hamilton Health Sciences Corporation through the Population Health Research Institute (PHRI)
What is That and Why is it There? Case Carousel

AMIT SHARMA
CARDIOLOGY FELLOW (PGY-5)
MONDAY APRIL 16th, 2018

OBJECTIVES

- Create a differential diagnosis for intra-cardiac masses
- Understand the indications for surgical intervention in infective endocarditis
- Describe the pathophysiology and management of myocardial aneurysms and pseudoaneurysms
DISCLOSURES

- I have no disclosures or conflicts of interest relevant to this talk

UT

- 41 year old male with no past medical history presented to the ED on 3/12/2018 with left ankle swelling and pain
- Traveled from Utah to Minnesota by car to visit his father
- On ROS, reported 4 months of night sweats, weight loss, and low grade fever
- Negative work-up, including infectious, in Utah
UT

- Vitals on admission to ED:
  - BP 149/42
  - HR 133
  - T 37.8
  - RR 22
  - O2 97% on RA
- Labs on admission to ED:
  - Creatinine 1.29
  - Hemoglobin of 8.8
  - Platelets 224
  - WBC 8.88
  - INR 1.2

Initial concern for cellulitis of left ankle given swelling and erythema but given atypical appearance, arthrocentesis performed with return of small amount of fluid.

CTPE study ordered and was negative for PE but notable for an enlarged LV.

Admitted to the hospital for further evaluation including TTE to further evaluate abnormal LV enlargement on CT.

CT of abdomen/pelvis showed splenomegaly with hypodense wedge shaped lesion concerning for infarct.
TTE on 3/13/18 showed aortic valve mass, question of bicuspid aortic valve, severe aortic insufficiency with pressure half time of 83 milliseconds, ascending aorta aneurysm of 4.4 cm, mitral valve mass, moderate mitral regurgitation, PASP 40 mm Hg + RAP, and dilated LV with LVEF 45-50%

Cardiology consultation requested

Initial cardiac examination notable for III/VI diastolic murmur along LSB, II/VI holosystolic murmur at apex, splinter hemorrhages in multiple nailbeds, and erythema/swelling of the left ankle

TEE ordered to further evaluate valvular abnormalities on TTE
UT

- TEE performed on 3/14/2018 showed bicuspid AV (fused left and right cusps), 1.1 x 0.7 cm mass on AV with prolapse into LVOT, severe AI with holodiastolic aortic flow reversal, 1.3 x 1 cm globular mass on atrial surface of anterior MV leaflet with flow communication into mass and LA consistent with leaflet perforation and aneurysm, moderate MR with systolic blunting but no flow reversal in all four PV’s, LV enlargement, and LVEF 50-55%
At this point, etiology felt to be endocarditis despite negative blood cultures and CV surgery consultation ordered.

During hospitalization, patient remained hemodynamically stable without evidence of CHF.

CV surgery recommended surgery on AV and MV but wanted to wait and see if BC’s turned positive.

Additional issue of traveling patient with no health insurance coverage in MN.

Eventually, blood cultures from 3/12/18 turned positive for Cardiobacterium hominis (HACEK organism residing in the mouth) and Propionibacterium acnes (skin organism).

Left ankle arthrocentesis fluid returned positive for Cardiobacterium hominis.

IV antibiotics had already been started and were narrowed to cover the above organisms (Ceftriaxone).

Due to insurance issues, the patient decided to travel back to UT with his family for surgical treatment.

Has been seen in ID and general medicine clinic follow up since discharge with no change in clinical condition.
Intra-cardiac Masses

- Masses can be characterized by their location, appearance, and associated signs/symptoms
- Often asymptomatic and detected incidentally while imaging for other reasons but depending on the etiology, can present with embolization, obstruction, valve destruction/regurgitation, direct myocardial/pericardial involvement, and constitutional/systemic symptoms
- Usual initial imaging modality is echocardiography followed by CT and MRI if further visualization and characterization required

Anatomical variants
- Implanted devices
- Thrombus
- Vegetation
- Tumors
  - Primary
  - Metastatic
- Artifacts
Intra-cardiac Masses

- Anatomical variants
  - Left Atrium: Pectinate muscles and warfarin ridge
  - Right Atrium: Crista terminalis, Eustachian valve, Chiari network, and catheter/device leads
  - Ventricles: Non-compaction and moderator/muscular bands
  - Valves: Excrescences and calcification
  - Pericardium: Cysts and fat
  - Atrial Septum: Lipomatous hypertrophy
Intra-cardiac Masses

- **Thrombus**
  - Most common intra-cardiac mass
  - Location usually within LV (post-MI and cardiomyopathy), LA (appendage > body), and RA (catheter/device related and PE “in transit”)
  - Often times discrete and/or spherical and usually located along the wall of intra-cardiac structure (LV or LA)
  - Clinical clues assist in diagnosis such as AF, MS, MI with apical hypo/akinesis, cardiomyopathy, and others
Massive LAA Thrombus

LV Apical Thrombus
LV Apical Thrombus

Intra-cardiac Masses

- Tumor
  - Can be located in atria, on valves, myocardium, and pericardium
  - Metastatic more common than primary cardiac tumor
  - Of primary cardiac tumors, benign more common than malignant
  - Most common overall and benign tumors are myxoma and papillary fibroelastoma
  - Most common primary malignant tumors are sarcomas
Tumors

- **Myxoma**
  - Most are sporadic but small % are familial (Carney complex)
  - Can arise anywhere in the heart but majority are connected to inter-atrial septum, are located on the atrial surface, and usually left > right atrium
  - Clinical presentation includes constitutional symptoms, embolization, or obstruction
  - Usually diagnosed incidentally during imaging for another cause
Tumors

- **Papillary Fibroelastoma**
  - Most common benign valvular tumor and usually located on the aortic valve
  - Most common manifestation is embolization
  - Can be confused with Lambl's excrescences
    - Lambl's located at sites of valve closure, may be multiple, and increasing incidence with increasing age
Tumors

- Benign: Rhabdomyoma, fibroma, lipoma, angioma, and others
- Malignant
  - Primary: Sarcoma
  - Secondary: Lung, breast, lymphoma, colon, and others

Intra-cardiac Masses

- Vegetations
  - Usually valvular or located on intra-cardiac device/leads or sites of prior intervention/surgery
  - Irregular and variable shape with hallmark being independent motion from that of the valve and density that is different from that of surrounding tissue
  - Location on valve and appearance can distinguish different types of vegetations (infective versus non-bacterial thrombotic)
  - Usually associated with valvular damage and regurgitation
  - Less likely to cause obstruction unless very large
  - Constitutional symptoms
Vegetations

Comparison of the four major forms of vegetative endocarditis. The rheumatic fever phase of rheumatic heart disease (RHD) is marked by small, warty vegetations along the lines of closure of the valve leaflets.

Infective endocarditis (IE) is characterized by large, irregular masses on the valve cusps that can extend onto the chordae.

Nonbacterial thrombotic endocarditis (NBTE) typically exhibits small, bland vegetations, usually attached at the line of closure. One or many may be present.

Libman-Sacks endocarditis (LSE) has small or medium-sized vegetations on either or both sides of the valve leaflets.

QT

- 39 year old male with a past medical history notable for OOH VT/VF arrest secondary to long QT syndrome (KCNQ1 positive) s/p secondary prevention ICD and paroxysmal atrial fibrillation
- Medications include Metoprolol XL 100 mg once daily + Flecainide 150 mg twice daily
QT

- Seen in cardiology clinic on 11/3/16 due to 10 weeks of fevers up to 102 degrees, chills, and night sweats
- Previously seen in multiple urgent cares, clinics, and by ID with negative work-up, including BC’s and CT chest imaging
- Multiple rounds of empiric antibiotics given with no improvement in clinical condition
- TTE ordered given intracardiac device and risk for infection
TTE showed a mobile echogenic mass measuring 2.4 x 3.4 cm on the ICD lead with mild associated IR but no obvious involvement of the TV

Admitted to the hospital for further evaluation and treatment
Vitals on admission to ED:
- BP 108/70
- HR 100
- T 37.5 → 39.5
- RR 18
- O2 98% on RA

Labs on admission to ED:
- Hemoglobin of 11.2
- WBC 13.14
- INR 1.4

Blood cultures drawn, broad spectrum antibiotics started, and ID/cardiology consulted.

Given the findings on TTE, a TEE was ordered to further evaluate the abnormal findings.
4/4 BC’s from 11/3/16 and 4/4 BC’s from 11/4/16 returned positive for Streptococcus mitis/oralis

Transferred to United Hospital on 11/6 for complex device and lead extraction by laser extraction

This was performed but complicated by embolization of thrombus to left main PA and secondary PEA arrest requiring thoracotomy and retrieval of clot

Transferred to the ICU on multiple vasopressors with rapid recovery and eventually discharged from the hospital with WCD as a bridge to re-implantation of ICD

Returned to HCMC on 1/4/2017 and underwent uncomplicated ICD implantation

Followed in cardiology clinic and has been doing well overall with no signs of recurrent device infection
Infective Endocarditis

- Defined as an infection of the endocardial surface of the heart, which usually involves the heart valves, in addition to intracardiac devices.
- Predilection for anatomically abnormal or foreign materials and surfaces such as damaged heart valves, bicuspid AV, prosthetic valves, shunts, and ICD’s/PM’s.
- Inciting event is bacteremia with common sources being oral, GI, and GU tracts.
- Constitutional symptoms may or may not be present initially and damage is caused via persistent bacteremia, embolic phenomenon, local tissue destruction including valvular regurgitation and abscess, and eventually congestive heart failure.

Infective Endocarditis

- Differences in left and right sided endocarditis:
  - Left sided: More common than right-sided, associated with acquired/congenital defects, higher rate of embolic complications and mortality, increased hemodynamic compromise, Staphylococci and Streptococci involved but others implicated as well, can involve either or both the aortic and mitral valve.
  - Right sided: Associated with IVDU, catheters/lines, and cardiac devices (PM and ICD), usually Staphylococcus aureus, better tolerated hemodynamically than left sided, majority of cases involve the tricuspid valve and less likely device (usually involves leads +/- generator but not tricuspid valve), more likely to respond to medical therapy alone compared with left sided IE.
Infective Endocarditis

- Lack of RCTs addressing issues in endocarditis specifically related to indications for surgery and timing of surgery and mostly come from observational studies.
- Guidelines and data are greater for left sided compared with right sided endocarditis with guidelines for right sided endocarditis being extrapolated from that in left sided endocarditis.

Indications for Surgery in Left Sided IE

- Valve dysfunction (usually regurgitation) causing significant symptoms of heart failure.
  - Largest mortality benefit seen in this group with moderate to severe valvular heart failure and this is most common reason for surgery.
- Endocarditis caused by aggressive and/or highly resistant organisms.
  - Staph aureus and lugdunensis, Pseudomonas, fungi (Candida and Aspergillus), Coxiella, Brucella, and VRE are examples.
  - Higher mortality with medical therapy alone in fungal and Staph aureus IE compared with surgery.
- Complicated by heart block, annular abscess, intra-cardiac fistula, or highly destructive lesions which are associated with increased mortality.
  - Most commonly seen with AV IE.
Indications for Surgery in Left Sided IE

- Evidence of persistent infection 5-7 days after initiation of appropriate antibiotic therapy and in the absence of alternative septic foci
- Recurrent emboli
  - Usually CNS but can be associated with any arterial bed including renal, splenic, bowel, and others
  - Most CNS emboli in MCA distribution
  - Highest risk of embolization is before diagnosis is made or within 2 weeks thereafter
  - Bigger vegetation = higher embolic risk
- Large size of vegetation with >10 mm being a common cut-off especially in the setting of embolism or >15 mm in absence of embolism (controversial)
  - Mobility is another consideration although this is subjective with high inter-observer variability
- Prosthetic valve endocarditis
Indications for Surgery in Right Sided IE

- Evidence of persistent infection 5-7 days after initiation of appropriate antibiotic therapy and in the absence of alternative septic foci
- Vegetation size > 20 mm
  - Some advocate size cut-off of 10 mm but this is controversial
- Recurrent septic pulmonary emboli
- Aggressive or resistant organisms (similar group as that for left sided IE)
- Severe right HF secondary to severe TR with poor response to medical therapy
  - Not as common an indication as for left sided IE
- All of the above have a class IIa and level C of evidence in ESC guidelines
Timing of Surgery

- **Emergent**
  - Generally defined as within 24 hours
  - Examples include refractory heart failure/pulmonary edema and/or cardiogenic shock

- **Urgent**
  - Defined as after 24 hours to within a few days
  - Uncontrolled infection, complicated endocarditis (heart block, abscess, fistula), enlarging vegetation, large vegetation size > 10 mm with prior embolization

- **Elective**
  - Usually done during the index hospitalization or in follow up after discharge
  - Patients should be on appropriate antibiotic therapy at the time of surgery and further delay of surgery for a “sterile field” is not beneficial
  - Challenges in different definitions of emergent, urgent, and elective across studies
  - Particular example is non-major CVA versus major CVA and hemorrhagic CVA and recommendation to defer surgery for at least 4 weeks in latter group due to risk of hemorrhagic transformation or worsening of hemorrhage with CPB associated anticoagulation

Early Surgery versus Conventional Treatment for Infective Endocarditis (EASE)

- 76 patients with left sided endocarditis, severe valve disease, and vegetation > 10 mm randomized to early surgery (within 48 hours) versus conventional treatment
- Primary end-point: Composite of in-hospital death and embolic events within 6 weeks of randomization
- Secondary end-point: Death from any cause, embolic events, recurrence of IE, and repeat hospitalization due to CHF
- Primary end-point significantly reduced with early surgery versus conventional treatment (1 patient versus 9 patients, HR 0.10, and P = 0.03) driven largely by reduction in embolization
- Criticized for low surgical risk and co-morbidities of population and lack of aggressive organisms (Staph aureus)
Surgical Principles

- Debridement and removal of all infected and necrotic tissue and vegetations in addition to foreign material in the case of prosthetic valve and/or device associated endocarditis
  - In device associated endocarditis, improved outcome with medical therapy + extraction compared with medical therapy alone
  - Repair is generally preferred to replacement, especially in IVDU with high risk of relapse and recurrent endocarditis
  - If prosthetic valve chosen, reasonable to use bioprosthetic valve in patients with intracranial bleeding, major CVA, or other contraindications to anticoagulation
  - In TV endocarditis, options include repair, replacement, and excision (valvulectomy)
    - Valvulectomy described by Arbulu limited to extreme cases in the setting of normal PA pressures and PVR and valve replacement is often needed at follow up

IE Guidelines

- Class I
  - Early surgery: Heart failure, fungi or highly resistant organisms, heart block, abscess, destructive/penetrating lesions, persistent bacteremia/sepsis, recurrent emboli (PVE guidelines similar to NVE)
  - Right Sided: Valve repair preferred over replacement
  - Antibiotics at the time of surgery
  - Complete removal of pacemaker and defibrillator systems including all leads and generator
IE Guidelines

Class IIa

- Early surgery: Recurrent emboli, enlarging/unchanged vegetations, mobile vegetations > 10 mm
- PVE: Relapsing infection
- Right sided: Surgical intervention is reasonable for patients with certain complications and avoidance of surgery in IVDU's
- CVA: Surgery should be delayed at least 4 weeks in patients with hemorrhagic or disabling ischemic CVA
- Anticoagulation: Discontinuation of all forms of anticoagulation, even in mechanical valves
- Complete removal of pacemaker and defibrillator systems including all leads and generator in IE caused by Staph aureus even in the absence of device infection

IE Guidelines

IIb

- Early surgery: Vegetations > 10 mm particularly with anterior MV leaflet involvement (class I in ESC guidelines), and isolated vegetation > 15 mm (ESC guidelines)
- CVA: Surgery should be considered in patients with CVA in the absence of hemorrhagic or disabling ischemic CVA
39 Year Old Female with Metastatic SCC
32 Year Old Male with Newly Diagnosed NHL
PA

- 55 year old male with no known past medical history admitted to the hospital following OOH VT/VF arrest
- Was having intercourse with significant other when he became unresponsive and EMS called
- Upon arrival, found to be in VT/VF requiring ACLS with eventual ROSC
- Intubated in the field
Vitals on admission to ED:
- BP 134/86
- HR 82
- RR 17
- O2 100% on RA

Labs on admission to ED:
- Hemoglobin 12.6
- Potassium 3.3
- Creatinine 1.85
- AST 487
- ALT 533
- Lactate 10.5
- Troponin 0.102
PA

- Taken emergently to coronary angiography given OOH VT/VF arrest
Coronary angiography findings:

- Left main: No CAD
- LAD: Type II vessel with mild luminal irregularities and 60% stenosis of small caliber D2
- Left circumflex: 50-60% stenosis in the mid vessel
- RCA: Moderate disease in the proximal/mid vessel and severe diffuse disease of distal RCA. TIMI II flow and no myocardial blush or washout. Left to right collaterals present.
- Bedside TTE after the procedure showed akinetic inferior wall with question of aneurysm/pseudoaneurysm

Admitted to ICU and underwent hypothermia protocol which was complicated by seizures and recurrent VT/VF arrest requiring Amiodarone infusion

TTE was ordered
Formal TTE showed LVEF of 30%, WMA of the inferior/inferolateral/apical regions with inferior aneurysm/pseudoaneurysm containing thrombus, and large LV thrombus.

Started on anticoagulation for LV thrombus.

On further questioning of the patient, he reported an episode of severe chest tightness that occurred two months prior to presentation with associated diaphoresis, nausea, and SOB for which he did not seek medical attention.

VT/VF arrest felt to be scar mediated from prior infarction involving the inferior wall.
- Poor neurologic function with rewarming initially but patient eventually made significant progress with limited neurologic disability
- A cardiac CT was ordered to further evaluate abnormal TTE findings
Multiple discussions held between CV surgery and cardiology with findings felt to be a pseudoaneurysm.

Although management for pseudoaneurysm is surgical, the patient was felt to be at high risk given his recent cardiac event, significant debility, and recovering neurologic function.

Plan made for serial imaging to re-evaluate the pseudoaneurysm.
Underwent placement of secondary prevention ICD on 12/30/2016

Discharged to acute rehabilitation facility on OMT for CAD and cardiomyopathy

Since then, serial TTE and cardiac CT has shown the pseudoaneurysm to be stable in size with decreasing burden of thrombus

Has made a full neurologic recovery and is back to working full time in IT

LV Aneurysm and Pseudoaneurysm

- Aneurysm
  - Thinned area of dyskinetic myocardium often accompanied by scar formation
  - Myocardium and endocardium present

- Pseudoaneurysm
  - Myocardial free wall rupture contained by pericardium
  - No myocardium or endocardium present

Aneurysm is more common than pseudoaneurysm

Important to distinguish accurately between the two entities given different natural histories and thus management
LV Aneurysm and Pseudoaneurysm

- **Etiology**
  - Most aneurysms and pseudoaneurysms are secondary to myocardial infarction, especially with delayed or incomplete revascularization
  - Other etiologies include post-cardiac surgery, trauma, and infection

- **Clinical Presentation**
  - Asymptomatic
  - Chest pain
  - Shortness of breath
  - Congestive heart failure
  - Ventricular arrhythmias
  - Embolic phenomenon due to thrombus within aneurysm/pseudoaneurysm cavity
  - Sudden cardiac death from rupture

- **Diagnosis**
  - Usually found as incidental finding on imaging ordered for another reason
  - EKG may show persistent ST elevation in area of original infarct
  - Gold standard for diagnosis is autopsy or surgical evaluation of aneurysm/pseudoaneurysm layers
  - Historically, angiography with ventriculography was the imaging modality of choice
  - TTE is now considered the initial diagnostic test of choice
  - Other modalities include TEE, CT, and MRI
  - No guidelines provided for follow up imaging after initial diagnosis

- **Neck**
  - Wide (aneurysm) versus narrow (pseudoaneurysm)

- **Location**
  - Aneurysm most common in anterior wall and apex
  - Pseudoaneurysm most common in inferior wall (rupture in anterior wall essentially fatal → unable to develop pseudoaneurysm)
LV Aneurysm and Pseudoaneurysm

Management

- Main goal of treatment is to prevent expansion and rupture along with treating signs/symptoms related to complications of aneurysm (heart failure, arrhythmia, embolism)
- Medical management is aimed at decreasing wall stress (Laplace's Law: $\text{wall stress} = \frac{\text{pressure} \times \text{radius}}{\text{wall thickness}}$) and preventing embolic complications
  - Blood pressure control and afterload reduction
  - Anticoagulation for thrombus (acute aneurysm/pseudoaneurysm has a higher risk of embolism than chronic and risks/benefits of anticoagulation to reduce thrombus and embolism must be weighed with increasing propensity for rupture)
- Traditionally, aneurysms have been managed non-surgically due to low risk of rupture compared with pseudoaneurysms which are managed surgically due to higher risk of rupture
  - Class IIa indication to consider aneurysmectomy + CABG in patients with intractable ventricular arrhythmias or heart failure refractory to medical and catheter-based therapy

Prior series looking at surgical and overall mortality were in the days preceding current medical therapy and revascularization (PCI and/or thrombolytics) and thus may not be accurate in contemporary era

Given the rarity of these conditions (especially pseudoaneurysm), there is a paucity of RCTs and thus guidelines to inform decision making and most studies are observational

Surgical mortality is lower now than in the past with the development of improvements in surgical technique

Rupture risk related to chronicity (acute versus chronic) and size (small versus large) of aneurysm/pseudoaneurysm
References