Review of Ongoing Trials in Cardiology

Suneet Mittal, MD
Chair, Cardiology
Director, Electrophysiology
The Valley Hospital
Ridgewood, NJ

www.valleyhealth.com/EP

8th Annual Comprehensive CV Disease Management: From Fundamentals to Innovation 2024
March 1, 2024
Disclosures: Consultant to Boston Scientific and Medtronic
Reasons We Engage in Research

- Innovation in patient care
- Improvement of treatment standards
- Professional development
- Reputation enhancement
- Financial incentives
- Demand from patients
- Regulatory requirements and partnerships
- Global health contributions
CONFIRM2 is an international, multicenter observational registry designed to comprehensively evaluate the relationship of CCTA findings (including coronary, non-coronary cardiac, non-cardiac vascular, and clinical variables) to future clinical outcomes in patients undergoing clinically indicated CCTA.

CONFIRM2 is projected to perform the largest cardiovascular phenotype outcomes study ever

- Up to 200,000 patients
- Up to 50 sites
- Global

No large multicenter study has examined the totality of information visualized by coronary CT angiography (CCTA) for optimal refinement of prognostic risk stratification.
Randomized comparison of the clinical Outcome of single versus Multiple Arterial grafts in Women: the ROMA:Women trial
Cardiac Surgery

SAG (Single arterial grafting)

1. LITA to LAD

2. SVG to main target vessel of lateral wall

MAG (Multiple arterial grafting)

1. LITA to LAD

2. RA or RITA to main target vessel of lateral wall

*L For revascularization of the right coronary artery, the use of additional arterial grafts or SVG is allowed in the MAG group, while only SVG is allowed in the SAG group.

ROMA-Women Trial (NCT: 04124120)
PI: Dr. Juan Grau
Cardiac Surgery

- Aim 1: Determine the impact of MAG vs SAG on major adverse cardiac and cerebrovascular events in women undergoing coronary artery bypass grafting (CABG)

- Aim 2: Determine the impact of MAG vs SAG on generic and disease-specific QOL, physical and mental health symptoms in women undergoing CABG
Electrophysiology

Hypertension Is Prevalent in Pacemaker Population
Drop in Systolic Blood Pressure May Have Significant Impact*

- Pacemaker patients are commonly older (average 70 yrs)
- HTN is the most common comorbidity, affecting >70% of pacemaker patients
- Majority have Isolated Systolic (ISH**) HTN, a more difficult to treat form of HTN
  - Elevated pulse pressure is an independent risk factor for cardiovascular events
  - Most therapies cannot effectively reduce pulse pressure resulting with difficult to treat population
- Patients have high rate of comorbidities
- Patients have higher risk of Cardiovascular disease

Potential Clinical Impact of a 10mmHg Drop in BP

- ~13% decrease in annual all cause mortality
- Lower risk of developing serious conditions
  - 20% decrease in rate of major cardiovascular disease events
  - 17% decrease in the rate of coronary heart disease
  - 27% decrease in the rate of stroke
  - 28% decrease in the rate of heart failure
- Improve patient QoL
  - Decreased rate of comorbidities creates indirect QoL benefits
  - AVIM therapy is used in conjunction with and believed not to compete with HTN SOCs (Lifestyle Changes, medications Etc.); potential for cumulative benefits

BACKBEAT Cardiac Neuromodulation Trial (NCT: 06059638)
PI: Dr. Suneet Mittal
Electrophysiology

Atrioventricular Interval Modulation (AVIM) Therapy

- Therapy designed to lower blood pressure (BP) while simultaneously modulating the Autonomic Nervous System
- Delivered using a dual-chamber pacemaker

Therapy is designed to:
- Have an immediate response
- Reduce blood pressure
- Have a sustained effect
- Be applicable to a broad range of hypertensive subjects
- Be programmable and adjustable

BACKBEAT Cardiac Neuromodulation Trial (NCT: 06059638)
PI: Dr. Suneet Mittal
AVIM Therapy showed encouraging results in MODERATO II, a prospective, multi-center, randomized, (AVIM Therapy + Medical Therapy vs. Continued Medical Therapy), double-blind, pilot study of pacemaker subjects with persistent hypertension.

**Significant Reduction in 24-Hr aSBP and oSBP**

- **Δ -11.1 mmHg** in 24-Hour aSBP at 6 months
- **0%** MACE vs. 9.5% in control group at 6 months
- **Δ -17.5 mmHg** in oSBP at 2 years
- **85%** of subjects with reduction in aSBP

**BACKBEAT Cardiac Neuromodulation Trial (NCT: 06059638)**
PI: Dr. Suneet Mittal

In alliance with

**Cleveland Clinic**
Heart, Vascular and Thoracic Institute
Factor XI inhibitors

- Congenital deficiency of FXI
  - provides protection from both arterial and venous thrombotic events
  - is rarely associated with spontaneous major bleeding (i.e., lower bleeding rates than with other factor deficiencies like Factor X)

- Studies with FXI knockout mice demonstrated
  - resistance to both venous and arterial thrombosis
  - no spontaneous or induced bleeding compared with wild-type mice
Primary Efficacy Objective
To evaluate if milvexian is non-inferior to apixaban for the composite of stroke and non-CNS systemic embolism (SE).

Secondary Objectives
- To evaluate if milvexian is superior to apixaban in reducing risk of the principal safety endpoint family:
  - ISTH major bleeding
  - Composite of ISTH major and CRNM bleeding
- To evaluate if milvexian is superior to apixaban for:
  - The composite of CV death (CVD), MI, stroke, and non-CNS SE
  - CVD
  - The composite of All Cause Death (ACD), MI, stroke, and non-CNS SE
  - The composite of CVD, MI, stroke, acute limb ischemia (ALI), and urgent hospitalization for vascular cause of ischemic nature (including thrombotic events: DVT and PE)
  - ALI is defined as any unanticipated revascularization or amputation of ischemic limb.
Electrophysiology

Age ≥ 18 and atrial fibrillation or atrial flutter and eligible for anticoagulation

Age ≥ 75

History of stroke

Has 2 or more:
- Age 65 to 74
- Hypertension
- Diabetes
- Vascular Dz (CAD, MI, PAD)
- Congestive Heart Failure

If no exclusions, ENROLL

LIBREXIA-AF (NCT: 05757869)
PI: Dr. Dan Musat
Current approach is one size fits all
We would like to introduce a “pill-in-pocket” approach

- Stop DOAC (Direct Oral Anticoagulant)
- Monitor intensively
- Anticoagulate PRN (“pill-in-pocket” OAC)
  - Targeted- in response to a prolonged Afib episode
  - Minimize exposure to OAC
  - Maintain stroke prevention

Electrophysiology

REACT-AF (NCT: 05836987)
PI: Dr. Suneet Mittal
Electrophysiology

- **1:1 randomized trial**
  - Chronic DOAC
  - Smartwatch-guided/targeted DOAC

- **Primary endpoint (non-inferiority)**
  - Ischemic stroke
  - Systemic embolism
  - All-cause mortality

- **Secondary endpoint (superiority)**
  - Major bleeds

- **5350 pts / 80-100 US sites**
- **Follow-up for 3-5 years**
Heart Failure

Guimaraes L et al. *European Cardiology Reviews* 2020
Heart Failure

- Prospective, multicenter, randomized, sham-controlled, double blinded, adaptive trial
- Subjects with chronic HF and preserved (EF ≥ 50%) or mildly reduced (40% ≤ EF < 50%) left ventricular ejection fraction (LVEF), who remain symptomatic despite appropriate GDMT
- Adaptive sample size ranging between 400 and 700 randomized subjects
- Patients will be randomized in a 1:1 ratio to the investigational device procedure or a sham-control procedure
- Up to 60 sites in the United States (US) and up to 40 sites outside of the US (Canada, Europe, Middle East, Australia and New Zealand)
- Study follow-up is through 5 years after the index procedure for all study subjects

https://youtu.be/JEsR6JqmR8M

The ALLAY-HF Trial (NCT: 05685303)  
PI: Dr. Raj Tayal

The Snyder Center for Comprehensive Atrial Fibrillation

Cleveland Clinic
Heart, Vascular and Thoracic Institute

Valley Health System
Heart Failure

VICTORIA Trial: vericiguat
NEJM 2020

Key Inclusion Criteria
1. LVEF <45%, NYHA Class II-IV
2. Recent HF event
   i. HFH within 6 months
   ii. Outpatient IV diuretics within 3 months
3. NT-proBNP > 1000pg/dL
4. Receiving currently available GDMT for HF

A Primary Outcome

No. at Risk
Placebo 2524 2053 1555 1097 772 559 324 170 0
Vericiguat 2526 2099 1621 1154 826 577 348 125 1

Hazard ratio, 0.90 (95% CI, 0.82-0.98)
P=0.02
Heart Failure

HFrEF with recent worsening

VICTORIA

HFrEF Risk without recent worsening

VICTOR

VICTOR HF Trial (NCT: 05093933)
PI: Dr. Marcus Williams
Structural Heart Disease

SAPIEN X4 System Features

- **Variable valve sizing** – each valve size (23, 26, 29) can be deployed across a range of diameters

- **RESILIA tissue leaflets** offer anti-calcification technology

- **Valve rotational control** for attempted commissural alignment

https://youtu.be/KR0TK5ZQy-o

The Alliance Trial (NCT: 05172960)
PI: Dr. Raj Tayal
Structural Heart Disease

SAPIEN 3 Ultra
4 valve sizes (~3 mm increments)

20 mm
23 mm
26 mm
29 mm

SAPIEN X4
16 Valve Diameters (~0.5 mm increments) achieved by 3 valve sizes

21.5 mm
23.5 mm
24.5 mm
26.5 mm
27.5 mm
30.0 mm

The Alliance Trial (NCT: 05172960)
PI: Dr. Raj Tayal
Structural Heart Disease

ALLIANCE Program

ALLIANCE Trial
Protocol: 2021-05
Symptomatic, Severe Aortic Stenosis of the Native Aortic Valve

Primary Endpoint: Non-hierarchical composite of death and stroke at 1 year

All-Risk Single Arm

Native (Trileaflet) n=765
Native Bicuspid n=150

Follow-up (Annually Through 10 years)

The Alliance Trial (NCT: 05172960)
PI: Dr. Raj Tayal
# Structural Heart Disease

## Grading AS Severity & Timing for Treatment

<table>
<thead>
<tr>
<th>ACC/AHA Guidelines</th>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic Jet Velocity (m/s)</td>
<td>2.0-2.9</td>
<td>3.0-3.9</td>
<td>≥4.0</td>
</tr>
<tr>
<td>Mean Gradient (mmHg)</td>
<td>&lt;20</td>
<td>20-39</td>
<td>≥40</td>
</tr>
<tr>
<td>Aortic Valve Area (cm²)</td>
<td>&gt;1.5</td>
<td>1.0-1.5</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

The Progress CAP Trial (NCT: 04889872)  
PI: Dr. Raj Tayal

[In alliance with Cleveland Clinic]
Structural Heart Disease

The Progress CAP Trial (NCT: 04889872)
PI: Dr. Raj Tayal
VHS Research in Cardiology

- High Clinical Trial Activity
- Efficient Trial Start-Up
- Strong Core of Investigators
- Residency Program
- Early Access to Novel Technologies And Therapies

Bluestar BioAdvisors