Research Update
(moving the flag forward)

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Objectives

• Discuss how research contributes to high quality care and health care delivery
• Outline the structure of the research program here at LGH
• Briefly review current studies and highlight some ongoing trials of general interest

Benefits of Lancaster General Health having an active research program:

• LGHEALTH beneficiaries will have access to innovative medical approaches through clinical trials conducted in their community.
• Medical advances will more rapidly be adopted and incorporated into standard care practices.
• The scientific rigor required by the conduct of research will have positive effects on the overall quality of medical practice in the community.
• Health care providers will be encouraged and empowered to remain on the cutting edge of their profession.
• Lancaster General Health will be able to attract physicians with academic backgrounds to Lancaster County and thereby advance the clinical expertise in our community.
Lancaster Research Institute Goals

• Develop evidence-based health practices
• Evaluate the safety and efficacy of new treatment modalities for the health conditions affecting our community
• Assess the clinical and cost-effectiveness of innovative methods for the delivery of health services
• Examine the effectiveness of existing treatments and care delivery systems

Resources: Funding

• Intramural
  - Von Hess
• Extramural
  - Corporate
    - Federal (NIH, CMS)
    - Isolated grants
  - Innovation Network
    - UPStart, AppITUP – Poisel
    - Hospital based - Rosin

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Director of Academic Affairs/Research
Manager research operations
Statistician/Data Programmer
Research Project Coordinator
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Barbara Martin, PhD
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Multicenter Clinical Trials
Physician/provider clinical research
Academic projects
Quality/Outcomes research

1/12/2017
Current Trials

- Oncology
- Bariatrics
- Nephrology
- Vascular and CT Surgery
- Gastroenterology
- Women's/Baby
- Family Medicine
- Neurology
- Endocrinology

Cardiology

- CAD
- EP
- CHF
- HTN
- PA HTN
- Imaging
- Risk factor

Enrolling: 28
Start up: 6
Follow up: 18

Physiology of HF symptoms

SMILE Trial
02-001

Background
- 88 y/o man
- ICM EF 20%
- CABG + AoVR (CE) ’13, PCI 3/16
- Severe MR
- Hyperlipidemia
- HTN
- SLE

02-001 – Admission 3/8-13/2016

Status
- SOB, cough
- BNP 1969
- CXRay = CHF
- PCI RCA + IABP
- BUN 25, creat .8
- Enrolled SMILE

Medications
- ASA 81/day
- Plavix 75/day
- Lipitor 10/day
- Coreg 3.125 BID
- Synthroid
- Protonix
- Flomax
- Plaquenil
- Lasix 80 am 40 pm

Discharge FU
- Enroll ortho and increase BUN
- DC pm Lasix
- Increase Lisinopril 5/day

02-001

Furosemide 120mg QD
Furosemide 80mg QD
Furosemide 40mg QD
Background

- 86 yo man
- HFpEF
- Acute and chronic renal insufficiency stage III
- s/p TAVR, 1/16
- CABG '92
- HTN
- Hyperlipidemia
- CRT-P
- DM
- Anemia

02-002

AdmissionFU

Discharge

Metolazone 2.5 mg PRN

Zaroxolyn 2.5 mg PRN

Furosemide 40 mg QD

Torsemide 50 mg QD

Extra

Demadex 20 mg
A Brief History of Cardiac Pacing

1928 - Lidwell (Australia) and Hyman (US) independently develop first artificial pacer

Advances in Pacemaker Systems

1956 - Leatham and Davies develop first external demand stimulator in the UK

Paul Zoll, a Boston cardiologist, ushers in the modern era of cardiac pacing with his external cardiac pacing device

A Brief History of Cardiac Pacing

First myocardial wire implanted in a 3yo following repair of TOF

Power failure lasting 3 hours results in tragic death of a baby's heart

Bakken develops partially implanted pacer with external battery

Senning/Elmqvist first totally implanted pacer in Arne Larsson who was having 20-30 episodes/day of syncope from AV block. Larsson died 12/01 of a malignancy having required 22 pulse generator replacements.

1958 - First totally implanted pacer

Leatham and Davies develop first external demand stimulator in the UK

Advances in Pacemaker Systems

Micra VVIR Pacemaker

• Intended for patients that have a Class I or II indication for a single-chamber ventricular pacemaker.

• Contraindicated in patients with current implanted cardiac devices which:
  - would interfere with the placement of the Micra device
  - are providing active cardiac therapy
Micra Implantable Device (Pacemaker)

- Size
  - Volume: 0.8 cc
  - Length: 25.9 mm
  - Outer diameter: 6.7 mm
  - Mass: 2.0 g
- Bipolar sensing/pacing
- Fixation mechanism: Nitinol tines
- Battery
  - Chemistry: Lithium silver vanadium oxide/Carbon monofluoride
  - Longevity: 7.1/9.6 year longevity (2.0/1.5V output, 60 bpm, 100% paced)
- Capabilities
  - VVIR
  - RV capture management
  - Sensing assurance
  - Diagnostics
- Device deactivated to OOO at end of life

Key Differences

The primary differences in functionality between Micra and standard single chamber pacemakers are:

- Rate response
  - Three axis accelerometer sensor
  - Located within the heart
- Capture management
  - Hourly safety margin to maximize longevity
  - Runs at either 0.24ms (nominal pulse width/chronaxie) or 0.4ms
- End of Service
  - Can be permanently programmed "OFF to OOO mode" (no pacing or sensing)
**Study Purpose**

- To evaluate the safety and efficacy of the Micra Transcatheter Pacing System and to assess long-term device performance.
- Support regulatory submissions around the world, including CE Mark and FDA approval.

**Enrollment/Follow Up Pathway**

**Primary Objectives**

*Study considered successful once both primary objectives are passed*

**Safety**

- Freedom from major complications* related to the Micra transcatheter pacing system and/or procedures at 6 months post-implant (within 183 days) > 83%

**Efficacy**

- At the Month 6 visit, > 80% of subjects with a pacing capture threshold ≤ 2 V at pulse width of ≤ 0.24 ms and stable (increase of ≤ 1.5 V)

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*Major complication is defined as any complication that results in death, permanent loss of device function due to a mechanical or electrical malfunction, hospitalization, prolongation of hospitalization for 24 or more hours, or system damage (removal, repackaging, un-replacement).
A Leadless Intracardiac Transcatheter Pacing System

Dwight Reynolds, M.D., Gabor Z. Duray, M.D., Ph.D., Razali Omar, M.D., Kyoko Soejima, M.D., Petr Neuzil, M.D., Shu Zhang, M.D., Mohammad Nazemeh, M.D., Charles C. Gornick, M.D., Petar Ivanovic, M.D., Petr R. Roberts, M.D., Venkata Sagi, M.D., John Hummel, M.D., Marco Ginario, M.D., Marcelo Benavides-Kitzmann, M.D., Edward J. N. Tait, M.D., Edward R. Friedland, M.D., Joseph B. Gaudio, M.D., Michael H. K. Leung, M.D., Olivier Ritter, M.D., Venkata Sagi, M.D., for the Micra Transcatheter Pacing Study Group

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Kaplan–Meier Estimate of Absence of Major Complications Related to the Micra System or Implantation Procedure through 12 Months after Implantation.

Electrical Performance Characteristics of the Transcatheter Pacing System, According to Study Visit.
Conclusions

- In this historical comparison study, the transcatheter pacemaker met the prespecified safety and efficacy goals. It had a safety profile similar to that of a transvenous system while providing low and stable pacing thresholds.

Heart Failure

- Heart failure is the leading cause of hospitalizations in patients aged 65 and older in the U.S. [1].
- Annually, >1 million patients are hospitalized with a primary diagnosis of heart failure [1].
- 20% of Medicare beneficiaries are re-hospitalized within 30 days of HF discharge [2].
- It is estimated that about 50% of these hospitalizations are unplanned and potentially preventable [2].

- High economic cost of recurrent hospitalizations account for over 75% of the $46 billion spent on HF in the US annually [3].

Diagnostics

- Traditional evaluation measures such as physical signs/symptoms and patient weight have been used to predict patients at risk for ADHF and are poorly associated with cardiovascular hemodynamics.
- These methods are administered intermittently and may not identify patients early enough to prevent ADHF [4].

- To reduce short-term readmissions and improve chronic disease management, the integration of multiple HF diagnostics is required and has been shown to identify patients at a higher risk of HF hospitalization [4,5,6,7].

References:
Weight Changes are Not Sensitive for Predicting Heart Failure Hospitalization

- > 10 lbs
- 3 - 5 lbs
- 6 - 10 lbs
- < 2 lbs

Chaudhry et al., Circulation 2007; 116:1549-54

Weight Changes are Not Sensitive for Predicting Heart Failure Hospitalization

Intrathoracic Impedance Monitoring

Ohm’s Law: R=V/I

Worsening HF → ↑ Fluid Retention → ↓ Impedance

↓ Filling Pressure

Rathman, Small. The Heart Group, Lancaster, PA
10/12/2015
Patient seen in HF clinic. +DOE; +6 pound weight gain. Volume overloaded on exam. Zaroxolyn added.
Diagnostics

- Prior studies have shown implantable device-measured diagnostics like intrathoracic impedance [8], AF burden, heart rate metrics [9], respiration [10], and patient activity metrics [11] can be used individually or in a combined fashion to identify when patients are at risk for HF events.

- We hypothesize that these measurements made in the subcutaneous thoracic space may be sensitive enough to detect physiological changes associated with ADHF.


- The use of implantable device features such as impedance is clinically useful in monitoring thoracic fluid status for pacemaker or ICDs and may be measured in the subcutaneous space.

- The Monitoring in Dialysis study was conducted in renal failure patients implanted with a Reveal LINQ™. Impedance trended upwards with fluid removal during dialysis sessions and downwards between dialysis sessions. The preliminary data show that continuous impedance monitoring has a direct inverse relationship to patient fluid status in both a detailed analysis and long term trending analysis [13].

![Reveal LINQ™ HF PHYSIOLOGIC DATA](image)
Study overview

PURPOSE

- The study is utilizing the Reveal LINQ™ device with an investigational LINQ™ HF RAMware download.

- LINQ™ HF RAMware enables the hardware to record and store impedance, temperature, activity, RR interval, R-wave amplitude, posture change count (based on z-axis accelerometer values) and x, y, and z-axis accelerometer measurements periodically.

- The purpose of the LINQ™ HF study is to characterize Reveal LINQ™ derived data from patients with heart failure by assessing the relationship between changes in LINQ™ derived data and other physiologic parameters with subsequent acute decompensated heart failure (ADHF) events.

Metabolism of lipoproteins in the presence of proprotein convertase subtilisin/kexin type 9 (PCSK9).”

Odyssey Trial

- In a randomized trial, alirocumab (a monoclonal antibody that inhibits PCSK9), as compared with placebo, reduced LDL cholesterol levels by an additional 52 percentage points.
- In a post hoc analysis, the incidence of cardiovascular events was reduced with alirocumab.

Original Article

**Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events**

Jennifer G. Robinson, M.D., M.P.H., Michel Farnier, M.D., Ph.D., Michel Krempf, M.D., Jean Bergeron, M.D., Ghislain Luc, M.D., Marcio Amare, M.D., Erik S. Strass, M.D., Ph.D., Gisle Langslet, M.D., Frederic V. Berne, M.D., Ph.D., Matthew El Shawabery, M.D., Michael J. Koren, M.D., Norman E. Lepor, M.D., Christopher Laurenzato, M.Sc., Robert Przyby, M.D., Unmesh Choudhari, M.D., John J.P. Kastelein, M.D., Ph.D., for the ODYSSEY LONG TERM Investigators
Conclusion

• Over a period of 78 weeks, alirocumab, when added to statin therapy at the maximum tolerated dose, significantly reduced LDL cholesterol levels.
• In a post hoc analysis, there was evidence of a reduction in the rate of cardiovascular events with alirocumab.

Hemodynamic monitoring:
CardioMEMS™
CardioMEMS™ HF System

PA Pressure Sensor on Catheter Delivery System

Patient Home Electronics Unit

PA Pressure Database

Received FDA approval on May 28, 2014

Wireless pulmonary artery hemodynamic monitoring in chronic heart failure: a randomized controlled trial CHAMPION


Case: 61 year old male; HFrEF

- PMH
  - HFrEF (EF 50%)
  - CAD s/p CABG with redo
  - MVR St. Jude
  - PAF
  - CKD stage 3
  - Hypothyroidism
  - Anemia – Hx GI bleed
  - CardioMEMSTM implant 5/12/2015

- Medications:
  - Eplerenone 50 mg BID
  - Isosorbide mononitrate 30 mg daily
  - Lisinopril 20 mg daily
  - Metoprolol succinate 50 mg daily
  - Torsemide 40 mg BID
  - Metolazone PRN

10 hospitalizations (9 HF related) the year prior to implant.
Case: 61 year old male; HFpEF

Pre-Implant 1 year 10 Hospitalizations/Observation
- 4/2014 TKR
- 9/2014 Hypokalemia
- 9/2014 CHF
- 10/2014 Hypokalemia
- 11/2014 Hypokalemia
- 11/2014 CHF
- 1/2015 CHF
- 2/2015 Hypokalemia, CP

Post-Implant 1 year 3 Hospitalizations/Observation
- 6/2015 Cellulitis right leg
- 7/2015 Septic knee
- 10/2015 Septic knee

CT PERFUSION

CT Perfusion offers the ability to assess anatomy and perfusion with one study.
Pharmacologic stress can be performed with Adenosine, Regadenoson or Dipyridamole.
Stress portion takes between 30 minutes – 45 minutes.
Needs a power contrast injector.
CT perfusion performed for 50% - 70% lesions by Coronary CTA.
Protocol for CT perfusion

- Coronary CTA's are ordered based on clinical indications.
- Patients with intermediate lesions (50% - 69%) are sent for CT perfusion to determine the hemodynamic significance of the lesion.
- Images acquired 2 minutes after the infusion of regadenoson during the administration of contrast.
- Rest and Stress images are compared, looking for defects at stress that are not present at rest.