Cardiac Rehabilitation: Current and Future Directions

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Disclosures

- There are no conflict of interests related to the products described in this talk
Overview of Talk

- The current state of cardiac rehabilitation
  - Outcome data supporting the use of cardiac rehabilitation
  - Cellular mechanisms associated with exercise
  - Intensive versus traditional cardiac rehabilitation
  - Barriers to utilization of cardiac rehabilitation

- Future directions in cardiac rehabilitation
  - Extending cardiac rehabilitation to the home through digital and wearable technologies to reduce readmission rates
  - Expanding scope of cardiac rehabilitation to HFPEF, POTS, PVD, and microvascular disease

- Our new program at UCSD
Cardiac Rehabilitation and Risk Reduction

Time to “Rebrand and Reinvigorate”

Pratik B. Sandesara, MD,* Cameron T. Lambert, MD,* Neil F. Gordon, MD, PhD, MPH,† Gerald F. Fletcher, MD,‡ Barry A. Franklin, PhD,§ Nanette K. Wenger, MD,* Laurence Sperling, MD*

ABSTRACT

Atherosclerotic cardiovascular disease (ASCVD) continues to increase annually in the United States along with its associated enormous costs. A multidisciplinary cardiac rehabilitation (CR) and risk reduction program is an essential component of ASCVD prevention and management. Despite the strong evidence for CR in the secondary prevention of ASCVD, it remains vastly underutilized due to significant barriers. The current model of CR delivery is unsustainable and needs significant improvement to provide cost-effective, patient-centered, comprehensive secondary ASCVD prevention. (J Am Coll Cardiol 2015;65:389-95) © 2015 by the American College of Cardiology Foundation.
CENTRAL ILLUSTRATION  Cardiac Rehabilitation and the ASCVD Prevention Pyramid

- **Second event**
  - **First event Clinical Disease**
    - Angina, MI, CHF, PAD, stroke, sudden death
  - **Subclinical Disease**
    - Left ventricular dysfunction, carotid stenosis, coronary calcification, myocardial ischemia, more vulnerable plaque, potential for thrombosis
  - **Traditional**
    - Age, family history, hypertension, dyslipidemia, diabetes, obesity
  - **Risk Factors**
  - **Nontraditional**
    - Psychosocial stressors, air pollution, inflammation, other (?)

- **Lifestyle Modification and Pharmacotherapies (if appropriate)**

- **Primary Prevention**
- **Unhealthy Lifestyle Practices**

- **Secondary Prevention**

- **Core components of Cardiac Rehabilitation**
  - Exercise Training
  - Patient Assessment
  - Nutrition Counseling
  - Weight Management
  - Blood Pressure Management
  - Lipid Management
  - Tobacco Cessation
  - Physical Activity Counseling
  - Psychosocial Management

- **Second event**

- **POOR DIETARY HABITS**
- **PHYSICAL INACTIVITY**
- **CIGARETTE SMOKING**

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Currently Covered Indications for Cardiac Rehabilitation (CR)

- Recent myocardial infarction (within 1 year)
- Post Percutaneous coronary intervention (PCI)
- Coronary artery bypass grafting (CABG)
- Chronic stable angina
- Cardiac transplantation
- Heart valve repair or replacement
- Stable, chronic heart failure (EF<35%)
Outcomes Associated with Cardiac Rehabilitation

- Meta-analysis of 34 randomized controlled trials showed that exercise-based CR programs are associated with:
  - A lower risk of reinfarction (OR 0.53; 95% CI: 0.38 to 0.76)
  - Decreased cardiac mortality (OR 0.64; 95% CI: 0.46 to 0.88)
  - Decreased all-cause mortality (OR 0.74; 95% CI: 0.58 to 0.95)

- CR reduces 90 day hospital readmission rate after acute MI or PCI
- Class IA recommendation by AHA/ACC Guidelines

### TABLE 1  Potential Cardioprotective Effects of Increased Lifestyle Activity, Structured Exercise, and/or Improved Cardiorespiratory Fitness

<table>
<thead>
<tr>
<th>Category</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-inflammatory</td>
<td>Reduced plasma level of C-reactive protein, which is a biomarker of inflammation (10)</td>
</tr>
<tr>
<td>Antithrombotic</td>
<td>Decreased platelet aggregation (11)</td>
</tr>
<tr>
<td></td>
<td>Enhanced fibrinolysis activity (12)</td>
</tr>
<tr>
<td>Antiarrhythmic</td>
<td>Improved cardiac autonomic function (13,14)</td>
</tr>
<tr>
<td></td>
<td>Increased vagal tone and decreased sympathetic activity (14)</td>
</tr>
<tr>
<td>Antiatherogenic</td>
<td>Improvement in established ASCVD risk factors</td>
</tr>
<tr>
<td></td>
<td>Improved endothelial function due to increased blood flow and shear stress on arterial walls (15,16)</td>
</tr>
<tr>
<td></td>
<td>Enhanced synthesis and release of nitric oxide, which is responsible for the inhibition of processes involved in atherogenesis (15)</td>
</tr>
<tr>
<td>Improved ASCVD</td>
<td>Decrease in total cholesterol, LDL-C, and triglycerides (17)</td>
</tr>
<tr>
<td>risk factors</td>
<td>Increase in HDL-C levels (17)</td>
</tr>
<tr>
<td></td>
<td>Reduced blood pressure (18)</td>
</tr>
<tr>
<td></td>
<td>Increased insulin sensitivity (19)</td>
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<tr>
<td></td>
<td>Weight reduction (19)</td>
</tr>
<tr>
<td>Anti-ischemic</td>
<td>Improved myocardial perfusion (20)</td>
</tr>
<tr>
<td></td>
<td>Raised ischemic threshold (11)</td>
</tr>
<tr>
<td></td>
<td>Ischemic preconditioning of the myocardium (21)</td>
</tr>
</tbody>
</table>
Cellular Mechanisms Associated with Exercise
- Improved mitochondrial function
- Increased nitric oxide production

**Figure 2.** Electron micrographs of cytochrome c oxidase in a patient with severe heart failure (left panel) and in a normal subject (right panel). Enzyme activity within the mitochondria (black) is reduced in heart failure.

Taub Clin Transl Sci. 2012
Cachexia of Heart Failure

HF patients have:
- Lower capillary density vs. normal subjects (due to low levels of nitric oxide)
- Shifts in muscle fiber types from the oxidative type I to the more glycolytic type II
- Decreases in mitochondrial oxidative enzymes (citrate synthase)
- The muscle wasting typically observed in HF patients, commonly referred to as cachexia, is associated with elevated levels of inflammatory biomarkers

Taub et al, Clin Sci 2013
Heart Failure
Patient with sarcopenia and muscle wasting
Exercise Training in CHF: Mortality and Morbidity Effects

- HF-ACTION
- RCT: usual care vs structured exercise training
  - 50 sites in US and Canada with 2331 patients enrolled
- 5 year follow-up
- Outcomes: death, hospitalization

*JAMA* 2009; 301:1439
Study Design

Chronic heart failure, NYHA Class II-IV, LVEF ≤ 35%, optimal medical therapy, and capable of exercising

Pre-randomization CPX and ECHO

Randomization 1:1
(_Stratified by center and HF etiology_

Usual Care

- Optimized medical treatment
- Patient education
- Phone calls
  
  **Recommendation:** Moderate intensity activity 30 minutes/day

Exercise Training

- Optimized medical treatment
- Patient education
- Phone calls
  
  **Supervised training**

  **Home training**
HF-ACTION Results

All-Cause Mortality or All-Cause Hospitalization

HR, 0.93 (95% CI, 0.84-1.02); \( P = .13 \)
Adjusted HR, 0.89 (95% CI, 0.81-0.99); \( P = .03^a \)

All-Cause Mortality

HR, 0.96 (95% CI, 0.79-1.17); \( P = .70 \)

CI indicates confidence interval; HR, hazard ratio.
\(^a\)Adjusted for key prognostic factors.

JAMA 2009; 301:1439
## Summary of Major Outcomes

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality and hospitalization (primary)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main analysis</td>
<td>0.93</td>
<td>0.84, 1.02</td>
</tr>
<tr>
<td>Adjusted analysis</td>
<td>0.89</td>
<td>0.81, 0.99</td>
</tr>
<tr>
<td>CV mortality and CV hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main analysis</td>
<td>0.92</td>
<td>0.83, 1.03</td>
</tr>
<tr>
<td>Adjusted analysis</td>
<td>0.91</td>
<td>0.82, 1.01</td>
</tr>
<tr>
<td>CV mortality and HF hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main analysis</td>
<td>0.87</td>
<td>0.75, 1.00</td>
</tr>
<tr>
<td>Adjusted analysis</td>
<td>0.85</td>
<td>0.74, 0.99</td>
</tr>
</tbody>
</table>
Barriers to Utilization of Cardiac Rehabilitation

- Fewer than 20% of all eligible patients participate in a CR
  - Of those who are referred to CR only 34% actually enroll
- Factors contributing to poor utilization
  1) lack of a centralized method for referral
  2) inadequate communication among treatment teams, patients, and CR facilities
  3) unfamiliarity with CR among potential referring physicians
  4) limited access, and perceived inconvenience for the patient (e.g. Copays)
Current Reimbursement for Cardiac Rehabilitation

- With the affordable care act there is a focus on preventive services
- There has been a gradual increase in reimbursement for cardiac rehabilitation
- Currently in California
  - Medicare: $107 per session
  - Commercial Payers (e.g. Anthem Blue Cross): $132 per session
  - For intensive cardiac rehab (ICR), 72 covered sessions
    - revenue is $7700 to $9500 per patient
## Ornish Versus Pritikin

<table>
<thead>
<tr>
<th>Total Number of Sessions covered 72 (max per day is 6 sessions) over 18 weeks</th>
<th>Ornish</th>
<th>Pritikin</th>
</tr>
</thead>
<tbody>
<tr>
<td>72 sessions (divided into 18 sessions that are 4 hours each)</td>
<td>72 sessions (can customize how many sessions per day)</td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>100% plant based</td>
<td>Allows for lean meat and fish</td>
</tr>
<tr>
<td>Format</td>
<td>All with live instructors: 1 hour of exercise 1 hour of nutrition counseling 1 hour of yoga and 1 hour of group therapy Patients are in groups of 10-12 and stay with the same cohort throughout the program</td>
<td>Some parts are Video Instruction. Sessions duration can be customized over 18 weeks</td>
</tr>
<tr>
<td>Outcome Data</td>
<td>The Lifestyle Heart Trial showed significant regression of coronary atherosclerosis measured by angiography in the experimental group randomly assigned to intensive lifestyle changes. (5 year results reported by Ornish JAMA 1998)</td>
<td>Data from Pritikin residential treatment centers showed improvement in lipids, A1c, blood pressure and weight. (Barnard Am J Cardiol 1992)</td>
</tr>
</tbody>
</table>
Lifestyle Heart Trial

% Diameter Stenosis: Quantitative Coronary Arteriography

Baseline (n.s.) 1y (P.02) 5y (P.001)

Case Study of a Patient from UCLA-Enrolled in ICR
New Paradigm For Cardiac Rehabilitation

- “Living Lab” for research and secondary prevention
- Ideal population to deploy new technologies to prevent readmission
  - Good outcome trials needed
- Using devices/wearables to expand the length and scope of cardiac rehabilitation
To Sense: CoVA Monitoring System

- Measures heart rate, heart rate variability, thoracic fluid levels (impedance), respiration rate
- Additional vitals and hemodynamic parameters (such as stroke volume and cardiac output values) will be added in future version of the CoVa™ Monitoring System
Dexcom:
Continuous Glucose Monitoring
Abbott: Freestyle Libre
Reflexion Health

- Tele-rehabilitation software platform that uses motion-tracking technology to coach patients through prescribed exercises.
“So, Doc, what would it take to make my little ‘problem’ disappear?”

“We need to replace your pinky ring with a wearable heart rate monitor.”
Fitness Trackers/Activity Monitors

Leading Manufacturers

• FitBit
• Nike+ FuelBand
• Garmin and Apple
Data on Fitness Trackers

• A randomized trial of 471 patients published in JAMA showed these fitness trackers had no impact on weight loss compared to control group.

• Studies has shown that there is inaccuracy in measurement of heart rate.
Beat-HF Trial

1437 hospitalized patients for HF were randomized

Intervention Arm: n=715 patients

Usual Care Arm: n=722 patients

Patients followed for 180 days

No difference in outcomes

Intervention:

• Combined health coaching telephone calls and telemonitoring (BP, HR and weight)
• Centralized registered nurses conducted telemonitoring reviews, protocoted actions, and telephone calls

Scripps Wired for Health Study

160 patients with hypertension, diabetes, or arrhythmia randomized

Intervention Arm: n=75 patients (monitored)

Control Arm: n=85 patients

Patients followed for 6 months

No difference in outcomes or costs
Scripps Wired for Health Study

- Members of the intervention group were issued an iPhone 4 and a connected device:
  - Hypertension: Withings blood pressure monitor
  - Diabetes: Sanofi IBGStar blood glucose
  - Arrhythmia: AliveCor ECG monitor

- Results
  - No difference in outcomes (BP, HBA1c between the groups)
  - No difference in health care costs or utilization as a result of the intervention

*PeerJ* 4:e1554 [https://doi.org/10.7717/peerj.1554](https://doi.org/10.7717/peerj.1554)
Mayo Clinic Study (Apps + Cardiac Rehab)

• 44 patients
  – 25 in the app + cardiac rehab arm
  – 19 in cardiac rehabilitation without the app arm

• The app tracked and monitored patient weight, BP, blood sugar and physical activity and provided educational content

• The app group had 40% less readmissions and lower blood pressure and weight
A large portion of cardiac rehabilitation strategies involves modifications to a patient’s lifestyle. Habits such as smoking, physical activity and exercise, diet, medications, and psychosocial well-being are all vital to improve heart health. By following good heart health habits on a daily basis, you can reduce your chance of a repeat heart attack. This profile serves as a daily guide toward improving heart health and well-being.
From: THE AUGMENTATION OF USUAL CARDIAC REHABILITATION WITH AN ONLINE AND SMARTPHONE-BASED PROGRAM IMPROVES CARDIOVASCULAR RISK FACTORS AND REDUCES REHOSPITALIZATIONS

Primary Results of the HABIT Trial
(Heart Failure Assessment With BNP in the Home)

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San Diego, Loma Linda, Banning, Orange, Mission Viejo, Irvine and Rancho Mirage, California

Objectives
This study was a multicenter, single-arm, double-blinded observational prospective clinical trial designed to monitor daily concentrations of B-type natriuretic peptide (BNP) and to determine how these concentrations correlate with acute clinical heart failure decompensation (ADHF) and related adverse clinical outcomes in at-risk HF patients.

Background
Although BNP at discharge is predictive of 30-day outcomes, outpatient serial testing may improve the risk of detecting early decompensation.

Methods
A total of 163 patients with HF signs and symptoms of ADHF discharged from the hospital or in an outpatient setting measured their weight and BNP levels daily for 60 days with a finger-stick test. Patients and physicians were blinded to BNP levels. The composite outcome was ADHF events: cardiovascular death, admission for decompensated HF, or clinical HF decompensation requiring either parenteral HF therapy or changes in oral HF medications.

Results
A total of 6,934 daily BNP values were recorded, with a median of 46 measures per patient over a monitoring period of 65 days. Forty patients had 56 events. Correlations between BNP measures weakened over time, and the dispersion between BNP measures grew. During 10,035 patient-days, there were 494 (4.9%) days of weight gain (≥5 lbs). The hazard ratio per unit increase of In BNP was 1.84, and the hazard ratio on a day of weight gain was 3.63. These effects retained significance when controlling for symptoms. When the monitoring period for each subject was broken into intervals based on ADHF events, there were 39 (18.4%) intervals of upward trending BNP corresponding to a risk increase of 59.8% and 64 (30.2%) downward trending intervals corresponding to a risk decrease of 39.0%. There were 94 (44.3%) intervals with 1 or more days of weight gain corresponding to a risk increase of 26.1%.

Conclusions
This pilot study demonstrates that home BNP testing is feasible and that trials using home monitoring for guiding therapy are justifiable in high-risk patients. Daily weight monitoring is complementary to BNP, but BNP changes correspond to larger changes in risk, both upward and downward. (Heart Failure [HF] Assessment with B-type Natriuretic Peptide [BNP] In the Home [HABIT]; NCT00946231) (J Am Coll Cardiol 2013;61:1726–35) © 2013 by the American College of Cardiology Foundation
Exercise Training for POTS

- Physical deconditioning (i.e., low stroke volume and reduced LV mass) and reduced standing stroke volume may be important to the pathophysiology of POTS

- Physical reconditioning with short-term exercise training significantly increased:
  - peak oxygen uptake,
  - expanded blood and plasma volume,
  - improved POTS orthostatic intolerance symptoms,
  - and in most cases allowed these patients to be symptom free
Study of Exercise in POTS

<table>
<thead>
<tr>
<th>Training type</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base pace (RPE 13–15)</td>
<td>10 × 30 min</td>
<td>6 × 30 min</td>
<td>5 × 35 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 × 35–40 min</td>
<td>4 × 45–60 min</td>
</tr>
<tr>
<td>Maximal steady state (RPE 16–18)</td>
<td>1 × 20 min</td>
<td>1 × 25 min</td>
<td>1 × 30 min</td>
</tr>
<tr>
<td></td>
<td>1 × 25 min</td>
<td>1 × 30 min</td>
<td>1 × 35 min</td>
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<tr>
<td></td>
<td>1 × 25 min</td>
<td>1 × 35 min</td>
<td>1 × 40 min</td>
</tr>
<tr>
<td>Recovery (RPE 6–12)</td>
<td>2 × 40 min</td>
<td>1 × 40 min</td>
<td>3 × 25 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 × 30 min</td>
<td></td>
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<tr>
<td>Strength training</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular modes</td>
<td>8 × 15–20 min</td>
<td>8 × 20–25 min</td>
<td>8 × 30 min</td>
</tr>
<tr>
<td>Recumbent bike Swimming</td>
<td></td>
<td>Month 1 modes plus</td>
<td></td>
</tr>
<tr>
<td>Rowing</td>
<td></td>
<td>upright bike</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Month 1 and 2 modes plus elliptical and treadmill walking</td>
<td></td>
</tr>
</tbody>
</table>

RPE = rating of perceived exertion (subjective rating of the entire cardio workout on a scale of 6–20: 6 is very, very easy; 11 is fairly easy; 13 is somewhat hard; 15 is hard; 17 is very hard; 19 is very, very hard).

- 103 patients completed the exercise program
Exercise Training in PAD

The magnitude of functional benefit derived from exercise training exceeds that observed in drug therapy trials with both pentoxifylline and cilostazol (Circulation. 2011;123:87-97)

<table>
<thead>
<tr>
<th>Table 2. Exercise Prescription for Supervised Endurance Training in PAD Patients With Intermittent Claudication</th>
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</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
</tr>
<tr>
<td><strong>Modality</strong></td>
</tr>
<tr>
<td><strong>Intensity</strong></td>
</tr>
<tr>
<td><strong>Duration</strong></td>
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<tr>
<td>Pathophysiological Process</td>
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<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>Arterial obstruction</td>
</tr>
<tr>
<td>Endothelial dysfunction</td>
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<td></td>
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<tr>
<td></td>
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<td></td>
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<tr>
<td>Mitochondrial dysfunction</td>
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<td></td>
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<tr>
<td>Inflammatory activation</td>
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</table>
Heart Failure with Preserved Ejection Fraction

- No proven therapies
- More common in women
- Heterogeneous disease
- Diastolic function is an energy-dependent process requiring ATP
- It is estimated that relaxation of the myocardium requires up to 15% of the total energy cost of the cardiac cycle
- In patients with HPEF, there is a decrease in the ratio of mitochondria to myofibrils and the function of the mitochondria is impaired
Microvascular Disease

- Mainly a disease of women
- Data from WISE study shows it is also associated with poor outcomes
- Associated with perfusion defect on SPECT/MRI
- Underlying mechanisms include endothelial dysfunction
- Studies underway to evaluate impact of exercise training
UC San Diego Health System Cardiac Wellness and Rehabilitation Program

Rehabilitation for patients with cardiac disease

Clinical Research focused on prevention, and patient centered mobile/wearable technologies

Wellness programs focused on lifestyle modification for all patients
Our center will facilitate unique research collaborations across UCSD
Microbiome and Diet

Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk

W.H. Wilson Tang, M.D., Zeneng Wang, Ph.D., Bruce S. Levison, Ph.D., Robert A. Koeth, B.S., Earl B. Britt, M.D., Xiaoming Fu, M.S., Yuping Wu, Ph.D., and Stanley L. Hazen, M.D., Ph.D.

ABSTRACT

BACKGROUND
Recent studies in animals have shown a mechanistic link between intestinal microbial metabolism of the choline moiety in dietary phosphatidylcholine (lecithin) and coronary artery disease through the production of a proatherosclerotic metabolite, trimethylamine-N-oxide (TMAO). We investigated the relationship among intestinal microbiota-dependent metabolism of dietary phosphatidylcholine, TMAO levels, and adverse cardiovascular events in humans.

METHODS
We quantified plasma and urinary levels of TMAO and plasma choline and betaine levels by means of liquid chromatography and online tandem mass spectrometry after a phosphatidylcholine challenge (ingestion of two hard-boiled eggs and deuterium (d9)-labeled phosphatidylcholine) in healthy participants before and after the suppression of intestinal microbiota with oral broad-spectrum antibiotics. We further examined the relationship between fasting plasma levels of TMAO and incident major adverse cardiovascular events (death, myocardial infarction, or stroke) during 3 years of follow-up in 4007 patients undergoing elective coronary angiography.

RESULTS
Time-dependent increases in levels of both TMAO and its d9 isotopologue, as well as other choline metabolites, were detected after the phosphatidylcholine challenge. Plasma levels of TMAO were markedly suppressed after the administration of antibiotics and then reappeared after withdrawal of antibiotics. Increased plasma levels of TMAO were associated with an increased risk of a major adverse cardiovascular event (hazard ratio for highest vs. lowest TMAO quartile, 2.54; 95% confidence interval, 1.96 to 3.28; P<0.001). An elevated TMAO level predicted an increased risk of major adverse cardiovascular events after adjustment for traditional risk factors (P<0.001), as well as in lower-risk subgroups.

CONCLUSIONS
The production of TMAO from dietary phosphatidylcholine is dependent on metabolism by the intestinal microbiota. Increased TMAO levels are associated with an increased risk of incident major adverse cardiovascular events. (Funded by the National Institutes of Health and others.)
Overall First Floor Plan
Landscape Site Plan
Cardiac Wellness & Rehab Center Overall Area

6,253 SF
Rendering of Patient Exam Room in Cardiac Wellness/Rehab Center
Rendering of Teaching Kitchen
Conclusions

- New era in cardiac rehabilitation ushered in by change in focus and reimbursement of our health care system
- Appropriate use of cardiac rehabilitation can lead to improved outcomes
- Expansion of cardiac rehabilitation to diseases such as HFPEF and POTS in the future
- Many digital health devices/apps but need good outcome data