MHIF Research Highlights: DECEMBER 2018

Notable Milestones & First Enrollments

- **Dr. Paul Sorajja**, National PI for early feasibility study of Left Atrial shunt implanted MHI’s first device on November 20th - assisted by Lynelle Schneider, PA. Congrats Team!

- **Dr. Karol Mudy** and team for enrolling 35 patients in the HeartMate LVAD clinical study; the product is now FDA approved!

FEATURED MHIF STUDIES
Open for Enrollment and Referrals!

- **ASAP-SVG** for coronary artery disease
  CONTACT: Pamela Morley, 612-863-6066

- **MINT** for myocardial ischemia & transfusion
  CONTACT: Rose Peterson, 612-863-6051

- **XIENCE 90** for patients at high risk of bleeding who need coronary stents
  CONTACT: Amy McMeans, 612-863-3895

MARK YOUR CALENDARS

Time to Run... or volunteer!

MHIF is proud to sponsor the Valentine’s 5K with Twin Cities in Motion. Mark your calendar!

Sat., Feb. 9, Lake Nokomis!

Raising Awareness of Valvular Disease!

MHIF is hosting a second annual Mechanics of a Healthy Heart event for patients.

Thurs, Feb. 21, Golden Valley Country Club!

SHOUT OUT TO...

**Drs. Hryniewicz, Grey & Saxena**
for participating in a heart-healthy discussion at The Marsh!

CONGRATULATIONS

To Dr. Stephen Bradley who published in JAMA Network Open:

“Hypothermia for Out of Hospital Cardiac Arrest”
2018 Cardiovascular Prevention Update

Michael D Miedema MD MPH
Director of Cardiovascular Prevention
Minneapolis Heart Institute
December 10, 2018

Objectives

- Aspirin
- Cholesterol Guidelines
- Diabetes
- Cardiovascular Genetics
3 Recent Large ASA Trials

- ASCEND
- ARRIVE
- ASPREE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

- 15,480 Individuals with diabetes but without known CVD
- Mean Age ~ 63 years
- Mean follow-up 7.4 years
- Aspirin 100mg vs placebo
A modest 12% relative risk reduction for a first serious vascular event

Figure 2. Effect of Assignment to Aspirin Group on Components of Serious Vascular Events, the Combined Outcome of Serious Vascular Event or Revascularization, and Major Bleeding and Its Components.
The New England Journal of Medicine

Original Article

Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly


19,114 Individuals age ≥ 70 years and free of CVD
100mg ASA vs Placebo
Median Follow-up 4.7 years

Hazard ratio, 0.95 (95% CI, 0.83–1.08)

Figure 1. Cumulative Incidence of Cardiovascular Disease.
<table>
<thead>
<tr>
<th>End Point</th>
<th>Overall [N=15,514]</th>
<th>Aspirin [N=9,052]</th>
<th>Placebo [N=5,462]</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of participants with event</td>
<td>rate per 1000 person-yr</td>
<td>no. of participants with event</td>
<td>rate per 1000 person-yr</td>
<td></td>
</tr>
<tr>
<td>Major hemorrhage†</td>
<td>626</td>
<td>8.6</td>
<td>265</td>
<td>6.2</td>
<td>1.38 (1.18–1.62)</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>179</td>
<td>2.5</td>
<td>72</td>
<td>1.7</td>
<td>1.30 (1.11–2.22)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>77</td>
<td>1.0</td>
<td>34</td>
<td>0.8</td>
<td>1.27 (0.81–2.09)</td>
</tr>
<tr>
<td>Subdural or extradural hemorrhage</td>
<td>61</td>
<td>0.9</td>
<td>22</td>
<td>0.5</td>
<td>1.79 (1.06–3.02)</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage‡</td>
<td>32</td>
<td>0.4</td>
<td>14</td>
<td>0.3</td>
<td>1.30 (0.64–2.60)</td>
</tr>
<tr>
<td>Extracranial bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper gastrointestinal bleeding</td>
<td>137</td>
<td>2.1</td>
<td>48</td>
<td>1.1</td>
<td>1.87 (1.32–2.66)</td>
</tr>
<tr>
<td>Lower gastrointestinal bleeding</td>
<td>127</td>
<td>1.7</td>
<td>54</td>
<td>1.3</td>
<td>1.36 (0.96–1.94)</td>
</tr>
<tr>
<td>Bleeding at another site§</td>
<td>189</td>
<td>2.4</td>
<td>88</td>
<td>2.1</td>
<td>1.16 (0.87–1.54)</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal major hemorrhage‡</td>
<td>52</td>
<td>0.7</td>
<td>24</td>
<td>0.6</td>
<td>1.18 (0.68–2.03)</td>
</tr>
<tr>
<td>Fatal hemorrhagic stroke</td>
<td>26</td>
<td>0.3</td>
<td>13</td>
<td>0.3</td>
<td>1.01 (0.47–2.17)</td>
</tr>
</tbody>
</table>

**Table 3. Major Hemorrhagic Events.**

**Death Related to Cancer**

- **Hazard ratio, 1.31 (95% CI, 1.10–1.56)**
- **No. at Risk**
  - Aspirin: 9525, 9481, 9408, 8286, 6291, 4016, 1495
  - Placebo: 9589, 9545, 9466, 8369, 6367, 4077, 1476
Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial

J Michael Gaziano, Carlos Rottenber, Brian Copplesi, Claude Cecuchs, Harold Dore, Philip S. Greenland, George Howard, Thomas A. Pearson, Peter Whellan, Lora Miguel-Asph, Wilma L. Tarumi, Gerard Sabourin; The ARRIVE Executive Committee

- 12,546 individuals at moderate CVD risk
  - Men > 55 years with 2 CVD risk factors
  - Women > 60 years with 3 CVD risk factors
- 10-year CVD Risk ~17%
- Median follow-up ~5 years
- ASA 100mg vs Placebo

Primary Outcome: 4.29% vs 4.48%, P-value 0.60
Any GI bleeding: 0.97% vs 0.46%, p-value 0.007

Myocardial Infarction: 1.52% vs 1.78%, p-value 0.23
Why the change in benefit?

- Change in Population


Dariush Mozaffarian et al. Circulation. 2015;131:e29-e322

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Why the change in benefit?

- Change in Populations

- Change in Outcomes

How does CVD first present?

[Image of a graph showing the age and sex distribution of 89,744 events in men and 54,754 in women representing the initial presentation of acute CVD with a wide range of settings. CVD includes coronary heart disease, stroke, cardiovascular disease, MI, and otherwise specified; and ECO, sudden cardiac death.]
Why the change in benefit?

- Change in Populations

- Change in Outcomes

- Change in Analysis

Per protocol Analysis

<table>
<thead>
<tr>
<th>Event</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>37 (0.98%)</td>
<td>72 (1.84%)</td>
<td>0.53 (0.36 –0.79); p=0.0014</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>32 (0.84%)</td>
<td>60 (1.53%)</td>
<td>0.55 (0.36 –0.84); p=0.0056</td>
</tr>
</tbody>
</table>

ARRIVE Trial, Lancet, 2018
Should we use ASA for primary prevention?

- Patients > 70 years
  - No
- Patients at low CVD risk
  - No
- Patients at elevated bleeding risk
  - No
- Patients 40-69 years old at elevated CVD risk who place a significant value on reducing CVD risk
  - Maybe

Objectives

- Aspirin
- Cholesterol Guidelines
- Diabetes
- Cardiovascular Genetics
2018 Cholesterol Guidelines - 4 Statin Groups

- Known ASCVD
- LDL-C >190mg/dl
- Individuals with Diabetes
- Primary Prevention – Elevated risk (>7.5%)
### Table 4. Very High-Risk* of Future ASCVD Events

#### Major ASCVD Events
- Recent ACS (within the past 12 mo)
- History of MI (other than recent ACS event listed above)
- History of ischemic stroke
- Symptomatic peripheral arterial disease (history of claudication with ABI <0.85, or previous revascularization or amputation)

### Table 4 continued

#### High-Risk Conditions
- Age ≥65 y
- Heterozygous familial hypercholesterolemia
- History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
- Diabetes mellitus
- Hypertension
- CKD (eGFR 15–59 mL/min/1.73 m²)
- Current smoking
- Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
- History of congestive HF
4 Statin Groups

- Known ASCVD
- LDL-C >190mg/dl
- Individuals with Diabetes
- Primary Prevention – Elevated risk (>7.5%)
Implications of Coronary Artery Calcium Testing Among Statin Candidates
According to American College of Cardiology/American Heart Association Cholesterol Management Guidelines

MESA (Multi-Ethnic Study of Atherosclerosis)

CAC distribution Across Spectrum of 10 Year Risk Score Among those >7.5% Risk Score

Nasir et al. JACC 2015

Event Rates only >7.5% in those with CAC>100

Nasir et al. JACC 2015
Other Considerations

- Monitor Response
  - Class 1 – LOE A

- Non-fasting lipid panels for routine screening

- Excellent evidence for statin safety
Recommendations for Statin Safety and Statin-Associated Side Effects

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>III: No Benefit</td>
<td>B-R</td>
<td>Coenzyme Q10 is not recommended for routine use in patients treated with statins or for the treatment of SAMS.</td>
</tr>
<tr>
<td>III: No Benefit</td>
<td>C-LD</td>
<td>In patients treated with statins, routine measurements of creatine kinase and transaminase levels are not useful.</td>
</tr>
</tbody>
</table>

Summary

Clinical ASCVD
- High Intensity Statin
- Goal LDL < 70mg/dl
- Very-High risk consider:
  - Ezetimibe
  - PCSK9

LDL > 190mg/dl
- High Intensity Statin
- Goal LDL < 100mg/dl
  - Ezetimibe
  - PCSK9

Diabetes
- Moderate Intensity Statin
- Consider high intensity if high risk

ASCVD Risk > 5%
- Moderate intensity Statin
- High intensity statin if high risk (>20%)
- If risk is 5-20% and decision is uncertain – consider CAC
• 8,149 Patients
• CVD or DM + other risk factors
• 4.9 years of follow-up
• On statin
• Elevated Trig’s

25% Relative risk reduction for CVD event (4.8% ARR)
### Summary

<table>
<thead>
<tr>
<th>Clinical ASCVD</th>
<th>LDL&gt;190mg/dl</th>
<th>Diabetes</th>
<th>ASCVD Risk &gt;5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High Intensity Statin</td>
<td>• High Intensity Statin</td>
<td>• Moderate Intensity Statin</td>
<td>• Moderate intensity Statin</td>
</tr>
<tr>
<td>• Goal LDL&lt;70mg/dl</td>
<td>• Goal LDL&lt;100mg/dl</td>
<td>• Consider high intensity if high risk</td>
<td>• High intensity statin if high risk</td>
</tr>
<tr>
<td>• Very-High risk consider:</td>
<td>• Ezetimibe</td>
<td>• Ezetimibe</td>
<td>• If risk is 5-20% and decision is uncertain – consider CAC</td>
</tr>
<tr>
<td>• Ezetimibe</td>
<td>• PCSK9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Consider Vascepa if elevated Triglycerides

### Objectives

- Aspirin
- Cholesterol Guidelines
- Diabetes
- Cardiovascular Genetics
Prevalence of Diabetes Mellitus

- ~12% of US Adults
- Significant heterogeneity across demographics (Figure)
- Type II DM accounts for 90-95% of all cases of DM in the US
- ~34% (81.6 million US adults) have pre-diabetes

Diabetes is a major risk factor for CVD

糖尿病是心血管疾病的主要风险因素。
Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Combined Mediterranean Diet</th>
<th>Control Diet</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-Value for Interaction</th>
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<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>117/2118</td>
<td>64/807</td>
<td>0.69 (0.51-0.94)</td>
<td>0.02</td>
</tr>
<tr>
<td>Female</td>
<td>72/2819</td>
<td>45/162</td>
<td>0.73 (0.53-1.01)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 yr</td>
<td>66/1322</td>
<td>47/504</td>
<td>0.75 (0.52-1.09)</td>
<td>0.14</td>
</tr>
<tr>
<td>≥70 yr</td>
<td>51/797</td>
<td>17/168</td>
<td>0.73 (0.51-0.98)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>54/2522</td>
<td>401/1801</td>
<td>0.67 (0.41-1.01)</td>
<td>0.03</td>
</tr>
<tr>
<td>Yes</td>
<td>12/2425</td>
<td>61/188</td>
<td>0.71 (0.53-0.96)</td>
<td></td>
</tr>
</tbody>
</table>
UKPDS

- 32% reduction in Primary Outcome
- 42% reduction in Diabetes-related death
- 36% reduction in All-cause Mortality
Insulin vs Insulin/Metformin

390 Patients with Type II DM on insulin randomized to metformin or placebo and followed for 4.3 years.

- Lower Hgb
- Lower A1C
- Less Insulin Use
- Lower BMI
- More significant improvements in A1C
- No associated weight gain
- Less Hypoglycemia
- Better CVD outcomes (compared to sulfonylureas)
Improve glycemic control - ? CVD Benefit

- Sulfonylureas
- Metaglinides
- DPP-4 Inhibitors
- Alpha glucosidase inhibitors
- Thiazolidinediones
- Insulin

Intensive Glucose Control ≠ Reduced CVD Events

ADVANCE Trial

11,140 Patients, A1C 6.5% vs 7.3%

VADT

1,791 Patients, A1C 6.9% vs 8.4%
Intensive Glucose Control ≠ Reduced CVD Events

ACCORD – Primary Outcome

ACCORD – ALL-Cause Mortality

10,251 Patients, A1C 6.4% vs 7.5%

*Significant weight gain in intensive group

Medications to reduce CVD risk

SGLT-2 Inhibitors

- Empagliflozin (EMPA-REG)
- Canagliflozin (CANVAS)
- Dapagliflozin (DECLARE)

GLP-1 Receptor

- Liraglutide (LEADER)
- Semaglutide (SUSTAIN-6)
- Albiglutide (Harmony)
SGLT-2 Inhibitors

- Reduction in Hgb A1C ~0.5-0.6%
- Decreased body weight
- Decreased BP
- Increased HDL
- Decreased triglycerides
- No hypoglycemia

Ahmed et al, EHJ 2017

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

- N=7,028
- Median Follow-up 3.1 Years
- Adults with type II DM and known CVD
- Mean age 63.1 years
- Mean Hgb A1C 8.1%
- Primary Outcome: CVD Death, non-fatal MI, non-fatal stroke
14% Reduction in Non-fatal MI, non-fatal stroke and CVD Death

38% Reduction in CVD Death
• N=10,142
• Median Follow-up 2.4 years
• Individuals with type II DM and CVD or high risk for CVD
• Mean Age 63 years
• Baseline A1C 8.2%
• Primary End-Point: Cardiovascular Death, non-fatal MI, non-fatal stroke
• 33% reduction in heart failure hospitalizations

The NEW ENGLAND JOURNAL of MEDICINE

ORIGIANAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes


• 17,160 patients
• 4.2 years follow-up
• Co-Primary End-Points
Figure 1. Major Cardiovascular and Renal Outcomes and Death from Any Cause.

**CENTRAL ILLUSTRATION:** Sodium-Glucose Co-Transporter-2 Inhibitors in Patients With and Without Cardiovascular Disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>With prior cardiovascular disease*</th>
<th>Without prior cardiovascular disease*</th>
<th>With prior cardiovascular disease*</th>
<th>Without prior cardiovascular disease*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.56 [0.44, 0.70]</td>
<td>0.56 [0.50, 0.63]</td>
<td>0.72 [0.63, 0.82]</td>
<td>0.61 [0.48, 0.78]</td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure=Death</td>
<td>0.63 [0.57, 0.70]</td>
<td>0.56 [0.50, 0.62]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Favor sodium-glucose co-transporter-2 inhibitors | Favor other glucose-lowering drugs

Glucagon-like Peptide-1 receptor agonists

- Reduction in Hgb A1C
- Weight Loss
- Decreased BP
- Decreased LDL
- Decreased inflammation
- GI side effects

Ahmed et al. EHJ 2017

Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

- N=9,340
- Median Follow-up 3.8 years
- Individuals with type II DM and CVD or high risk for CVD
- Mean Age 63 years
- Baseline A1C 8.2%
- Primary End-Point: Cardiovascular Death, non-fatal MI, non-fatal stroke
MHIF CV Grand Rounds – Dec. 10, 2018

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bani, M.D., Agostino Consoli, M.D.,
Freddy G. Eliaschewitz, M.D., Esedjian Ijide, M.D., Lawrence A. Leber, M.D.,
Bilko Lingoy, M.D., Stephen J. H. M.P.H., M.S.C. S., Julio Rosenstock, M.D.,
Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D.,
Olef Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Petterson, M.D., Ph.D.,
and Tina Vilsholt, M.D., D.M.Sc., for the SUSTAIN 6 Investigators

- N=3,297
- Median Follow-up 2.1 years
- Individuals with type II DM and CVD or high risk for CVD
- Mean Age 62 years
- Baseline A1C 8.7%
- Primary End-Point: Cardiovascular Death, non-fatal MI, non-fatal stroke

SUSTAIN 6 Trial, NEJM, 2016

*Increased risk for GI side effects
Objectives

- Aspirin
- Cholesterol Guidelines
- Diabetes
- Cardiovascular Genetics
Figure 1: 10-Year Coronary Event Rates, According to Lifestyle and Genetic Risk in the Prospective Cohorts.

Shown are standardized 10-year cumulative incidence rates for coronary events in the three prospective cohorts, according to lifestyle and genetic risk. Standardization was performed to cohort-specific population averages for each cohort. The 1 bars represent 95% confidence intervals.

A. Prevalence of a Familial Hypercholesterolemia Mutation Among Severely Hypercholesterolemic Individuals (LDL Cholesterol ≥190 mg/dl)

Controls of the Myocardial Infarction Genetics Consortium Studies
LDL ≥190: 430 of 8,577 (5%)

Participants of the CHARGE Consortium
Population-based Studies
LDL >190: 956 of 11,908 (8%)

FH Mutation
8 of 430 (1.9%)

16 of 956 (1.7%)

Khera et al, JACC, 2016
B. Impact of Familial Hypercholesterolemia Mutation Status on Coronary Artery Disease According to LDL Cholesterol Level

- Ref
- No
- Yes


A genomic risk score for coronary artery disease
Greater association with future coronary artery disease than any single conventional risk factor
Independent of yet complements conventional risk factors
Provides meaningful lifetime risk estimates of coronary artery disease
Quantifiable at or before birth and shows potential for risk screening in early life

Summary

- Aspirin for primary prevention
  - Should not be routinely used
  - Can be considered in select high risk patients
  - Should generally be avoided in elderly populations
- Cholesterol
  - Statin – ezetimibe – PCSK9 for individuals at high ASCVD Risk
  - CAC scoring for those who are uncertain about their risk
- Diabetes
  - Consider SGLT-2 inhibitor or GLP-1R for individuals with type II DM at high ASCVD risk
- Polygenic risk scores
  - Not quite ready for clinical use
  - But likely will be soon
Thank you