Phase 3 program of the oral factor eleven A inhibitor asundexian as novel antithrombotic

Currently Enrolling!
AF is a growing problem with greater morbidity and mortality

FXa Inhibitor Use is Rapidly Growing!

Guidelines recommend FXa inhibitors for patients with venous thromboembolism and atrial fibrillation

Over 6 million patients are currently on FXa inhibitors in the US

~6 M people with AF in U.S., expected to more than double by 2030

5x greater risk of stroke with AF


Current Therapies

• Current Antithrombotic Options
  - Aspirin
    - Meta-analysis (8 trials, 4876 participants), reduced stroke by 22% (6-35%)
    - Major bleeding risk 0.23%/year
  - Warfarin
    - Meta-analysis (6 trials, 2900 participants), reduced stroke by 64% (95% CI, 49-74%)
    - Major bleeding risk ~6%
  - Aspirin and Plavix
    - Pooled analysis (5 studies involving 24,084 participants) reduced stroke vs. aspirin alone (p<0.05)
    - Increased risk of major bleeding (p<0.05)

• Direct Oral Anticoagulants
  - Compared to warfarin
    - Dabigatran – lower ischemic stroke
    - Apixaban/edoxaban – lower hemorrhagic stroke and major bleeding
    - All DOACs – lower ICH

Bleeding complications!
Antidote cost!
Annual Hospitalizations for Major Bleeds\(^1\)

\[117,000\]

Annual Deaths Related to Major Bleeds\(^2\)

\[20,000\]

---

**Rocket AF and Aristotle Trials**

<table>
<thead>
<tr>
<th></th>
<th>Major Bleed (%/Year)</th>
<th>ICH (%/Year)</th>
<th>GI Bleed (%/Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban (ROCKET-AF)</td>
<td>3.6%</td>
<td>0.5%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Apixaban (ARISTOTLE)</td>
<td>2.13%</td>
<td>0.33%</td>
<td>0.76%</td>
</tr>
</tbody>
</table>

\(^{1}\) Truven Health Analytics, 12 months ending December 31, 2016 for Commercial, Medicare and Medicaid pts.

\(^{2}\) Skaistis J, et al. | *PLOS One* | 2015;10(9);e0137444.

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FXIa Inhibitor History

- Preclinical
  - FXI-deficient mice studies → benefit in reduced thrombus formation with no increase in bleeding time (even when given with dual antiplatelet agents), as seen in DOAC models.\(^1\)
  - Inherited FXI deficiency → lower clinical aPTT and categorized as mild bleeding phenotype with no direct association between activity levels and bleeding risk.\(^2\)
    - A lower stroke risk was particularly evident in patients with AF.\(^4\)
- Phase 1 studies
  - no relevant bleeding events were reported, shown to be safe and well tolerated.\(^3\)
- Phase 2 studies
  - Less bleeding compared to apixaban in AF patients, with some also receiving antiplatelet therapy
  - PACIFIC studies → n=4164, support for Asundexian 50mg dose selection, lower incidence of bleeding than apixaban, and potential benefit in prevention of ischemic strokes and TIA.


Asundexian: Mechanism of Action

Through selective inhibition of the intrinsic pathway, asundexian may prevent pathological clot formation (thrombosis) without hindering hemostasis (physiologic response to injury).
### OCEANIC-AF Endpoints

#### Objectives

<table>
<thead>
<tr>
<th><strong>Efficacy</strong></th>
<th><strong>Safety</strong></th>
<th><strong>Net clinical benefit</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Asundexan is superior to apixaban for prevention of stroke or SE</td>
<td>Asundexan is superior to apixaban as assessed by ISTH major bleeding</td>
<td>Compare the effects of asundexan and apixaban with respect to benefit and risk</td>
</tr>
</tbody>
</table>

#### Endpoints

<table>
<thead>
<tr>
<th><strong>Efficacy</strong></th>
<th><strong>Safety</strong></th>
<th><strong>Net clinical benefit</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of stroke or systemic embolism</td>
<td>ISTH major bleeding</td>
<td>Composite of stroke, systemic embolism or ISTH major bleeding</td>
</tr>
</tbody>
</table>

#### Secondary Objectives

- **Efficacy**: Compare the effects of asundexan and apixaban with respect to composite and individual efficacy endpoints
- **Safety**: Compare asundexan and apixaban with respect to composite and individual bleeding endpoints
- **Net clinical benefit**: To compare the benefit and risk of asundexan and apixaban with respect to a composite of efficacy and safety endpoints

<table>
<thead>
<tr>
<th><strong>Efficacy</strong></th>
<th><strong>Safety</strong></th>
<th><strong>Net clinical benefit</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of ischemic stroke or systemic embolism</td>
<td>Composite of ISTH major or CRNM®</td>
<td>Composite of stroke, systemic embolism, or ISTH major bleeding, or all-cause mortality</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Clinically relevant non-major bleeding</td>
<td>Composite of disabling stroke (mRS ≥ 3), critical bleeding, or all-cause mortality</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>Intracranial hemorrhage</td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>Fatal bleeding</td>
<td></td>
</tr>
<tr>
<td>Composite of CV death, stroke, or MI</td>
<td>Minor bleeding</td>
<td></td>
</tr>
</tbody>
</table>
OCEANIC-AF Risks

<table>
<thead>
<tr>
<th>Potential Risk of Clinical Significance</th>
<th>Summary of Data and Rationale for Risk</th>
<th>Mitigation Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>A risk for bleeding cannot be excluded in participants with AF included in the Phase 3 study and randomized to aspirin or to the comparator's aspirin.</td>
<td>Bleeding is the main safety concern related to anticoagulant therapies. For an inhibitor of Xa, lower bleeding risk is expected than with the comparator drug.</td>
<td>Exclusion criteria are planned to exclude patients with a history of bleeding or other anticoagulant therapy.</td>
</tr>
<tr>
<td>Liver-related adverse effects.</td>
<td>The findings regarding liver-related adverse events were consistent during the PACIFIC Phase 2 studies. Liver-related adverse effects will continue to be monitored to further characterize the clinical profile of aspirin.</td>
<td>Patients with known significant liver disease or known hepatic insufficiency will be excluded. Patients with Child-Pugh B or C will be excluded. Liver parameters are part of the standard laboratory panel and follow-up will be required for certain liver events. Furthermore, an IDMC will be installed monitoring unblinded study data on an ongoing basis.</td>
</tr>
</tbody>
</table>

Study drug will be discontinued if:

- ALT/AST > 8 x ULN
- ALT/AST > 5 ULN for 2+ weeks
- ALT/AST > 3 ULN and (total bilirubin >2 x ULN or INR 1.5)
- ALT/AST > 3 ULN with appearance of fatigue, nausea, vomiting, RUQ pain/tenderness, fever, rash, and/or eosinophilia (>5%)
Non-invasive approach to coronary microvascular disease diagnosis

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Director, Cardiovascular Imaging Research Center and Core Lab
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Personal Disclosures:
- Consultant (4C Medical, Abbott Structural, Anteris, AriaCV, Boston Scientific, Edwards Lifesciences, JenaValve, Medtronic, VDyne, WL Gore, Xylocor)
- Research Collaborations (Siemens Healthineers, Dr. Peter Kellman, NIH/NHLBI)
- Research Grant: Abbott Structural, Boston Scientific, Edwards Lifesciences, Abbott Northwestern Hospital Foundation
- Co-Investigator for SUMMIT Trial, Triluminate (sponsor: Abbott)

Imaging Core Lab:
- Research Support: Circle CV Imaging, Medis, 3Mensio
- Research Grants: Siemens Healthineers, Ziosoft

“All that wheezes is not asthma…”
“All that causes angina/ischemic chest pain is not epicardial CAD.

Symptoms and signs of myocardial ischemia with angiographically normal coronaries
Why is this important!?

2/3 of women who present with symptoms of chest pain and ischemia (angina), have **no** evidence of obstructive disease.
Impaired vasodilation (vasomotor abnormality) is important determinant \(\rightarrow\) ROS + oxidative stress

- Structural alterations \(\rightarrow\) reduction in flow due to the "environment" \(\rightarrow\) compression of the microvasculature (myocardial fibrosis, edema, etc.)

**References:**
**Figure 6: Conceptual Illustration of Overlapping Phenotypes in CMD and Potential Therapeutic Strategies**

- **A Patient Subgroups**
  - CMD
  - IOCA
  - CMP
  - CKD
  - Insulin Resistance
  - Obesity
  - HFpEF
  - Women
  - INOCA

- **B Potential Therapies**
  - Coronary Revascularization
  - Cardiac Transplantation
  - Device Therapy
  - Neprilysin Inhibitor
  - Statin
  - PCSK-9 Inhibitor
  - SGLT-2 Inhibitor
  - GLP-1 Agonist
  - Gastric Bypass
  - Anti-Inflammatory Therapy

(A) CMD phenotypes. (B) Potential therapeutic strategies. CKD - chronic kidney disease; CMP - cardiomyopathy; GLP - glucagon-like peptide; HFpEF - heart failure with preserved ejection fraction; INOCA - ischemia and no obstructive coronary artery disease; IOCA - ischemia and obstructive coronary artery disease; PCSK-9 - pro-protein convertase subtilisin/kexin type 9; SGLT = sodium-glucose cotransporter.

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**Diagnostic Criteria for Microvascular Angina and Vasospastic Angina in INOCA Patients**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Microvascular Angina</th>
<th>Vasospastic Angina</th>
</tr>
</thead>
</table>
| 1. Symptoms of myocardial ischemia | Effort or rest angina | Nitrate-responsive angina during spontaneous episodes, with at least one of these:
|          |                      | a. Rest angina, especially between eight and early morning
|          |                      | b. Marked diurnal variation in exercise tolerance, reduced in evening
|          |                      | c. Hyperventilation can precipitate an episode
|          |                      | d. Calcium channel blockers suppress episodes |
| 2. Absence of obstructive CAD (≥50% diameter reduction or FFR < 0.80) | Coronary CTA Invasive coronary angiography | Coronary CTA Invasive coronary angiography |
| 3. Objective evidence of myocardial ischemia | Presence of reversible defect, abnormality or flow reserve on a functional imaging test | Transient ischemic ECG changes during spontaneous episodes, including any of the following in at least two contiguous leads:
|          |                      | a. ST elevation ≥0.1 mV
|          |                      | b. ST depression ≥0.1 mV
|          |                      | c. Non-critical E waves |
| 4. Evidence of coronary dysfunction | Impaired coronary flow reserve (0% or 0%-2.5 depending on methodology used), invasive or non-invasive determined |
|          | Coronary microvascular spasm, defined as reproduction of symptoms, ischemic ECG shifts but no epicardial spasm during adenosine-induced pacing |
|          | Abnormal coronary microvascular resistance index (e.g., RR × Δ2)
|          | Coronary slow flow phenomenon, defined as TIMI frame count >25 |
|          | Coronary artery spasm, defined as transient total or subtotal coronary artery occlusion (≥95%) with angiographically normal coronary anatomy during spontaneous episodes |

*Definition:* All four criteria are met; *suspected* if criteria 1-2 are met but only criteria 3 or 4 are present or equivocal. **CMD:** coronary artery disease; **CTA:** computed tomographic angiography; **FFR:** fractional flow reserve; **RR:** index of microvascular resistance; **TIMI:** thrombolysis in myocardial infarction.
Association of CFR with MACE in several subgroups:
- Acute Coronary Syndromes
- Chronic Coronary Syndromes
- Heart Failure
- Heart Transplant
- Diabetes Mellitus
- Aortic Stenosis
- Systemic Sclerosis
- Sepsis
### Impaired CFR/MPRI Predicts CVD Outcomes in INOCA

**A**

**Invasive CFR**

Women with No Obstructive CAD

**B**

**PET CFR**

**C**

**CMR MPRI**

![Image of graphs and tables showing outcomes](chart.png)
PET: the gold standard for the non-invasive measurement of myocardial blood flow

PET with H\textsubscript{2}\textsuperscript{15}O or \textsuperscript{13}NH\textsubscript{3} allows accurate, reproducible and non-invasive measurement of absolute (ml/min/g) myocardial blood flow in man

Accuracy of PET MBF measurement

Reproducibility of PET MBF measurement

In humans

74yo female (BMI=24) with h/o COPD, HTN, prior COVID, mild coronary calcification with exertional dyspnea
Check Myocardial Blood Flow Quantification - Always Available!

68yo female (BMI=36) with h/o dyslipidemia, HTN, type 2 DM, CACS=1111 AU with exertional dyspnea. 50 lbs weight loss with.
Stress MBF = 1.7 ml/min/g
MPR = 2.1


V/M ratio 9.7

FFR 0.70

V/M ratio 26

FFR 0.96

MRI cardiovascular stress testing

myocardial perfusion imaging  quantitative perfusion mapping

visual assessment:
- time consuming
- subjective

quantitative assessment:
- rapid
- objective

Kellman P et al, JCMR 2017; 19:43

Quantitative Perfusion Improves Identification of 3V CAD

(moco) images  quantitative maps

Stress

Rest

normal subject  single vessel disease  triple vessel disease

18 of 53
Perfusion Maps improve interpretation accuracy

6 slice coverage is now feasible without compromise of the quantification/temporal or spatial resolution.

Increases coverage with dedicated 2-chamber.
**Validation against coronary physiology**

Aim

To assess the performance of CMR perfusion mapping for the diagnosis of MVD in patients with NOCAD

*Kotecha T .... Fontana M et al, JACC Imaging 2019*

---

**CMR Quantitative Perfusion Correlates well with Cardiac PET**


N=21 patients
CMR Quantitative Perfusion Correlates well with Cardiac PET


3 Vessel CAD unmasked by quantitative perfusion by both CMR and PET

Circulation

ORIGINAL RESEARCH ARTICLE

The Prognostic Significance of Quantitative Myocardial Perfusion: An Artificial Intelligence–Based Approach Using Perfusion Mapping

What Is New?
- Perfusion mapping uses artificial intelligence to provide instantaneous quantification of myocardial perfusion by cardiovascular magnetic resonance.
- Quantitative myocardial blood flow provides incremental prognostic information in patients with suspected coronary artery disease above traditional cardiovascular risk factors.
- Even in patients without regional perfusion defects, absolute perfusion is prognostic.

What Are the Clinical Implications?
- Absolute perfusion quantification is a likely new biomarker in patient care.
- As there is no user input and no ionizing radiation, early disease and microvascular disease can be studied at scale.
- Impaired global perfusion may be a targetable cardiovascular risk factor.

- Automatically AI-derived MBF and MPR have prognostic relevance beyond the detection of regional ischemia.
- Opportunity for quantitative perfusion analysis to be applied in the routine clinical setting to potentially risk stratify beyond the detection of regional ischemia alone.
- MACE was defined as myocardial infarction, stroke, heart failure admission, revascularization, or death.
- Revascularization events <90 days after CMR were excluded to prevent the inclusion of events occurring as a result of the perfusion CMR.

Our Cardiac MRI labs (ANW/United) can now detect this problem, with no additional radiation!
Clinical Case

- 75yo female with HTN, dyslipidemia, obesity (BMI=37), prior gastric bypass, CACS=187 AU, presenting with exertional dyspnea and vague retrosternal CP

SPECT IMPRESSION:
1. There is a small area of mild ischemia in the mid and apical anterior septum.
2. Normal left ventricular ejection fraction of 65 percent.
Adenosine 170 mcg Stress

25 y.o. female with a history of HTN, DM2 (not on medication), PCOS admitted on 10/2020 with CHF.
Future Directions

72yo female s/p OHTx in 2016 with 20% mid LAD non-obstructive stenosis thought to be cardiac allograft vasculopathy
Patients were classified into 2 groups according to the total MBFR: >2.0 and ≥2.0. An MBFR value of 2.0 was chosen as the cutoff based on the definition of microvascular dysfunction, prognostic value for stress PET and ROC (1.96).

Then classified into 3 CAV groups:
- Epicardial CAV + ischemia (SDS ≥ 2 or ISHLT CAV ≥ 2, MBFR > 2.0; Microvascular CAV: MBFR ≤ 2.0 and no ischemia or epicardial CAV; and Mixed CAV.

Patients with a microvascular flow reserve (MBFR) below 0.8 had a 7-fold increased risk of death or re-embolization, 12-fold increased risk of cardiovascular (CV) death or re-embolization, and 11-fold increased risk of CV hospitalization.

<table>
<thead>
<tr>
<th>All Patients</th>
<th>MBFR ≥ 2.0</th>
<th>MBFR &lt; 2.0</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 50</td>
<td>879 (69.6)</td>
<td>200 (66.7)</td>
<td>0.20</td>
</tr>
<tr>
<td>Age &gt; 60</td>
<td>202 (30.4)</td>
<td>100 (33.3)</td>
<td>0.20</td>
</tr>
<tr>
<td>Male</td>
<td>351 (50.8)</td>
<td>151 (49.2)</td>
<td>0.51</td>
</tr>
<tr>
<td>Women</td>
<td>542 (49.2)</td>
<td>185 (50.8)</td>
<td>0.51</td>
</tr>
<tr>
<td>CAD</td>
<td>490 (68.4)</td>
<td>140 (45.2)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Non-CAD</td>
<td>208 (29.6)</td>
<td>280 (84.8)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Total microvascular flow reserve</td>
<td>0.0018 (0.92)</td>
<td>0.18 (0.87)</td>
<td>0.0018</td>
</tr>
<tr>
<td>Nitroglycerin resistance, %</td>
<td>0.07 (0.15)</td>
<td>0.07 (0.15)</td>
<td>0.07 (0.15)</td>
</tr>
<tr>
<td>Any ischemia</td>
<td>0.07 (0.15)</td>
<td>0.07 (0.15)</td>
<td>0.07 (0.15)</td>
</tr>
<tr>
<td>Transected stenosis diameter, %</td>
<td>0.07 (0.15)</td>
<td>0.07 (0.15)</td>
<td>0.07 (0.15)</td>
</tr>
<tr>
<td>Coronary calcium</td>
<td>0.07 (0.15)</td>
<td>0.07 (0.15)</td>
<td>0.07 (0.15)</td>
</tr>
</tbody>
</table>

P value: 0.28 Table 2
BACKGROUND

Between March and September 2021, patients who met the criteria for acute TS with mid-apical regional wall motion abnormalities (WMA) and no significant coronary artery obstruction were approached to participate.

After informed consent, patients underwent comprehensive Adenosine stress CMR study with cine imaging, T2-mapping, quantitative perfusion with automated in-line quantification of global and regional MBF, in addition to late gadolinium enhancement (LGE) imaging. Same protocol was repeated at 6-months from initial CMR exam to assess for interval changes.

A total of 4 patients were so far recruited. All women, age range 49-77 years, with clear emotional trigger and mild troponin elevation (Table 1).

CMR was performed within 3 ± SD (or median, IQR) days from presentation. Left ventricular ejection fraction was 30-45% with regional myocardial edema (Figure 1) and hypokinesis or akinesis in the mid-apical segments (Figure 2). LGE was absent in all patients.

In the acute TS setting, although global rest (>1.0 ml/min/g) and global stress MBF (>2.0 ml/min/g) were normal, apical stress MBF was abnormal with a base/apex ratio >1.5 (normal=1.0) (Table 1) (Figure 3).

Repeat CMR at 6 months from acute presentation in 3/4 patients, has so far demonstrated resolution of myocardial edema, normalization of LV contractility and of stress MBF (Figures 1, 2, 3).

RESULTS

STRESS MYOCARDIAL BLOOD FLOW IS ABNORMAL DURING ACUTE TAKOTSUBO SYNDROME

Coronary microvascular dysfunction (CMD) is a proposed mechanism for takotsubo syndrome (TS).

To date, it is unknown whether changes in stress myocardial blood flow (MBF) exist during acute TS presentation, their associated mechanisms and the natural course of such abnormalities.

In a proof-of-concept mechanistic study, cardiac magnetic resonance imaging (CMR) with T2 mapping and quantitative stress perfusion were used to comprehensively evaluate during the acute TS presentation and at 6 months later.

METHODS

STRESS MYOCARDIAL BLOOD FLOW IS ABNORMAL DURING ACUTE TAKOTSUBO SYNDROME

• Coronary microvascular dysfunction (CMD) is a proposed mechanism for takotsubo syndrome (TS).
• To date, it is unknown whether changes in stress myocardial blood flow (MBF) exist during acute TS presentation, their associated mechanisms and the natural course of such abnormalities.
• In a proof-of-concept mechanistic study, cardiac magnetic resonance imaging (CMR) with T2 mapping and quantitative stress perfusion were used to comprehensively evaluate during the acute TS presentation and at 6 months later.

RESULTS

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CMR was performed within 3 ± SD (or median, IQR) days from presentation. Left ventricular ejection fraction was 30-45% with regional myocardial edema (Figure 1) and hypokinesis or akinesis in the mid-apical segments (Figure 2). LGE was absent in all patients.

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Repeat CMR at 6 months from acute presentation in 3/4 patients, has so far demonstrated resolution of myocardial edema, normalization of LV contractility and of stress MBF (Figures 1, 2, 3).

CONCLUSIONS

During acute TS, rest MBF is normal in all segments despite abnormal mid-apical contraction.

During acute TS, regional MBF response to adenosine stress is decreased in abnormally contracting LV segments.

This abnormal response may reflect intrinsic CMD or the consequence of regional myocardial edema.

At 6 months after acute event, wall motion, myocardial edema, and myocardial blood flow completely normalize.

Stress CMR may offer insights into the mechanism for TS.

Table 1 – Baseline Clinical and Imaging Characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>60</td>
<td>61</td>
<td>77</td>
<td>67</td>
</tr>
<tr>
<td>Basal troponin (ng/dL)</td>
<td>1.986</td>
<td>11.047</td>
<td>4.257</td>
<td>0.228</td>
</tr>
<tr>
<td>Ballooning Type</td>
<td>Apical</td>
<td>Apical</td>
<td>Apical</td>
<td>Apical</td>
</tr>
<tr>
<td>Left ventricular %</td>
<td>44</td>
<td>45</td>
<td>34</td>
<td>50</td>
</tr>
<tr>
<td>Type of TS stenosis</td>
<td>Emotional</td>
<td>Emotional</td>
<td>Emotional</td>
<td>Emotional</td>
</tr>
<tr>
<td>Stress MBF (ml/min/g)</td>
<td>2.3</td>
<td>2.5</td>
<td>2.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Basal segments</td>
<td>3.0</td>
<td>3.3</td>
<td>3.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Apical segments</td>
<td>1.8</td>
<td>1.5</td>
<td>1.4</td>
<td>1.7</td>
</tr>
<tr>
<td>Base to Apex Ratio</td>
<td>1.7</td>
<td>2.2</td>
<td>2.4</td>
<td>1.6</td>
</tr>
</tbody>
</table>
What did we study?

- Microvascular resistance reserve (MRR) (De Bruyne, Pijls et al. 2021) is the ratio of true resting microvascular resistance to hyperemic microvascular resistance:
  \[ MRR = \frac{R_{\mu,rest}}{R_{\mu,hyper}} = \frac{Q_{max}}{Q_{rest}} \cdot \frac{P_{a,rest}}{P_{d,hyper}} \]

- MRR is a reflection of disease only in the microcirculation, even in the presence of epicardial disease
  - MRR in the "normal" group was 3.4 compared with a mean MRR of 1.9 in the "abnormal" group.
  - MRR >2.7 ruled out coronary microvascular dysfunction (CMD) with a certainty of 96%, whereas MRR <2.1 indicated the presence of CMD with a similar high certainty of 96%.

What did we study?

- The CCTA+FFR\textsubscript{CT} pathway enables non-invasive evaluation of epicardial disease
  - We propose a non-invasively computed MRR (MRR\textsubscript{CT}) using a model built from CCTA imaging, and using total LV flow at rest and stress from [15O]H_2O-PET MPI
  - As a proof-of-principle, we evaluated MRR\textsubscript{CT} and FFR\textsubscript{CT} in different patient groups
0   Add animations

1   Explain the importance of MRR, and why evaluating microvascular resistance is important

2   Replace text with illustrations ideally, and explain clinical relevance

3   Explain how MRR-CT and FFR-CT allows us to evaluate epicardial and microvascular disease non-invasively

4   Add table showing how certain metrics would typically require invasive measurements (FFR for epicardial, MRR for microvascular evaluation), with a new row showing how we can do this non-invasively
What are the essential results?

- By tuning only total LV flow in our model, territory-level flow correlates strongly with \( [15O]H_2O \)-PET

\[
\begin{align*}
\text{Rest MBF} & = Q_{LV}^{\text{rest}} \\
\text{Hyperemic MBF} & = Q_{LV}^{\text{hyper}}
\end{align*}
\]

- \( MRR_{CT} \) was significantly different between disease categories, with the lowest values found in CMD patients, and highest values in Normal patients.

- \( MRR_{CT} \) displays a range of values for CAD patients, which could stratify patients for treatment.

<table>
<thead>
<tr>
<th>Disease Category</th>
<th>( MRR_{CT} )</th>
<th>FFR_{CT}</th>
<th>FFR</th>
<th>MRR_{CT}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (FFR&gt;0.8, \text{hMBF} \geq 2.3, \text{CFR} \geq 2.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAD (FFR \leq 0.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Funct. CMD (FFR \leq 0.8, \text{hMBF}&lt;2.3, \text{CFR}&lt;2.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Struct. CMD (FFR \leq 0.8, \text{hMBF}&lt;2.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

| 70 y.o. Female with typical angina, CMD, No CAD, and low MRR_{CT} |
|-----------------|----------|----------|-----|
| \text{FFR}_{CT} | 0.95 | 1 | 2.10 |
| \text{FFR} | 0.90 | 0.94 | 2.22 |
| \text{MRR}_{CT} | 0.98 | 1 | 2.10 |

| 58 y.o. Male with atypical angina, CAD, CTO and low MRR_{CT} |
|-----------------|----------|----------|-----|
| \text{FFR}_{CT} | 0.91 | 1.3 | 4.08 |
| \text{FFR} | 0.47 | 0.43 | 4.00 |
| \text{MRR}_{CT} | 0.90 | 0.91 | 4.18 |

| 55 y.o. Female with atypical angina, CAD, CTO and low MRR_{CT} |
|-----------------|----------|----------|-----|
| \text{FFR}_{CT} | 0.68 | 0.72 | 2.22 |
| \text{FFR} | 0.72 | 0.73 | 2.15 |

EuroPCR.com
Animate cases to appear 1 at a time

Point out that predicted MBF distribution of simulated polarmaps match well with the PET imaging, where we can see clearly the local perfusion deficits

Patient 1: mention patient conditions, highlighting normal epicardial vessels

Add any additional clinical context for the patient in a pop-up box in the purple section at the bottom

Update MRR -> MRRct in plot (bottom left)
The essentials to remember

CCTA-derived Microvascular Resistance Reserve (MRR\textsubscript{CT}) enables non-invasive evaluation of coronary microvascular function

- **Why?** MRR overcomes issues with CFR and IMR for evaluating CMD, but is invasive
- **What?** MRR\textsubscript{CT} is a non-invasive MRR assessment as derived from CCTA and PET MPI
- **How?** MRR\textsubscript{CT} uses geometry from CCTA, total LV rest and stress flow from MPI, and is computed at measurement sites from the resulting simulated pressure and flow
- **Results?** MRR\textsubscript{CT} distinguishes Normal subjects from CMD patients, and stratifies CAD patients into those with normal vs abnormal microvascular function
- **Why is this important?** MRR\textsubscript{CT} is the first non-invasive and specific approach to CMD

Closing Thoughts

- CMD is common (25-40%) of patients without obstructive CAD and symptoms. Female:male ratio (3:1). Comorbidities increase the risk.
- Stress Cardiac PET has been validated decades ago and accurate detection of CMD. Quantification with stress MBF and CFR (MPR) are reimbursable and available. Importantly, strongly linked with comorbidities and outcomes.
- Stress Cardiac MRI with now in-line automated quantitative perfusion - akin to stress PET - is available on both campuses and opens the possibility to provide objective assessment of CMD.
- Several new developments in imaging will continue to add value to this complex field and ultimately benefiting patients by providing an answer and tailored targeted medications.
Diagnostic evaluation of microvascular dysfunction and coronary spasm in the cardiac catheterization laboratory

Yader Sandoval, MD, FACC, FSCAI
Interventional Section, Minneapolis Heart Institute, Abbott Northwestern Hospital
Center for Coronary Artery Disease, Minneapolis Heart Institute Foundation, Minneapolis, MN.
Adjunct Associate Professor of Medicine, Mayo Clinic College of Medicine and Science
DISCLOSURES

- Abbott Diagnostics (advisory board), Roche Diagnostics (advisory board, speaker), Zoll (advisory board), Phillips (advisory board), Patent #20210401347 (machine learning models for ECG-based troponin level detection)

Nomenclature: INOCA and MINOCA

CorMicA: Coronary Microvascular Angina RCT

Eligible patients
Obstructive coronary disease excluded by angiography ± FFR
Cardiologic questionnaire

Randomize
n = 150

Catheter Laboratory Protocol
Left ventricular end-diastolic pressure
Diagnostic tests of coronary function
1) Coronary guidewire – FFR, IMR, CFR,
2) Pharmacological tests – ACh (10⁻⁶, 10⁻⁵, 10⁻⁴ M), GTN 30 worthy
Left anterior descending or other coronary artery

n = 75
Coronary Function Test-guided
Coronary function disclosed
(Guideline-based intervention group)

n = 75
Angiography-guided
Coronary function not disclosed
(Standard care group)

CONCLUSIONS
Coronary angiography often fails to identify patients with vasospastic and/or microvascular angina. Stratified medical therapy, including an IDP with linked medical therapy, is routinely feasible and improves angina in patients with no obstructive CAD. (CORONary MiCrovascular Angina CorMicA, NCT03193294) (J Am Coll Cardiol 2018;72:2841-55) © 2018 by the American College of Cardiology Foundation.

Guideline recommended (class 2) approaches for MVD

1. For patients with persistent stable chest pain and nonobstructive CAD and at least mild myocardial ischemia on imaging, it is reasonable to consider invasive coronary function testing to improve the diagnosis of coronary microvascular dysfunction and to enhance risk stratification.11

2a B-NR

2. For patients with persistent stable chest pain and nonobstructive CAD and stress PET MPI with MBFR is reasonable to diagnose myocardial dysfunction and to enhance risk stratification.8,11

2a B-NR

3. For patients with persistent stable chest pain and nonobstructive CAD and stress CMR with the addition of MBFR measurement is reasonable to improve diagnosis of coronary myocardial dysfunction and for estimating risk of MACE.12-14

2a B-NR

4. For patients with persistent stable chest pain and nonobstructive CAD and stress echocardiography with the addition of coronary flow velocity reserve measurement may be reasonable to improve diagnosis of coronary myocardial dysfunction and for estimating risk of MACE.15

2b C-EO

Non-invasive assessments of coronary/myocardial blood flow.

Doppler Echocardiography (class 2b)

Cardiac PET (class 2a)

Cardiac MRI (class 2a)

Doppler (class 2a)

Thermodilution (class 2a)
Coronary angiography and microvasculature

Imaging resolution

<table>
<thead>
<tr>
<th>30 μm</th>
<th>300 μm +</th>
</tr>
</thead>
</table>

Modified clinical classification of CMD

<table>
<thead>
<tr>
<th>CMVD</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Primary, i.e. in the absence of structural heart disease</td>
</tr>
<tr>
<td>Type 2</td>
<td>In the presence of cardiomyopathies such as LVH, HCM, DCM, amyloidosis.</td>
</tr>
<tr>
<td>Type 3</td>
<td>In the presence of obstructive CAD (including ACS)</td>
</tr>
<tr>
<td>Type 4</td>
<td>After coronary interventions</td>
</tr>
<tr>
<td>Type 5</td>
<td>After cardiac transplantation</td>
</tr>
</tbody>
</table>

Modifiers

<table>
<thead>
<tr>
<th></th>
<th>Acute or chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>Asymptomatic or symptomatic</td>
</tr>
<tr>
<td>Symptoms</td>
<td>None, minimal, moderate, or maximal level</td>
</tr>
<tr>
<td>Therapy</td>
<td>None, minimal, moderate, or maximal level</td>
</tr>
</tbody>
</table>

Invasive evaluation of microvascular dysfunction

Noninvasive testing more prevalent
**Invasive assessment more comprehensive**

Ischemia and No Obstructive CAD (INOCA)

Factors that increase likelihood of INOCA:
- Diabetes
- Hypertension
- Left ventricular hypertrophy
- Small coronary vessel size or luminal stenosis
- Inflammation
- Diabetic

Stable Chest Pain
Suspected INOCA

Noninvasive testing more prevalent
Invasive assessment more comprehensive

---

MHIF Cardiovascular Grand Rounds | May 22, 2023
Invasive evaluation of microvascular function and coronary spasm

Testing

- Non-endothelium dependent microvascular function
- Endothelium dependent vasomotion assessment
- Adenosine & coronary flow reserve
- Acetylcholine for spasm provocation

Conditions

INOCA

MINOCA

What is coronary flow reserve (CFR)?

CFR relates to the ability of the coronary circulation to increase blood flow in response to alterations in oxygen demand.
Available methods for invasive microvascular evaluations

Doppler

Thermodilution


Doppler Flow Velocity

- Flow velocity is extracted from these data by detecting the instantaneous peak velocity, which represents the maximum velocity within the sample volume.
- The average of instantaneous peak velocity over one or multiple heartbeats is termed average peak velocity (APV).

Escaned & Davies. Physiological assessment of coronary stenoses and the microcirculation.
### Normal diagnostic parameters: Doppler-based approach

<table>
<thead>
<tr>
<th></th>
<th>Non-endothelium dependent function (CFRne)</th>
<th>Epicardial endothelial function</th>
<th>Microcirculatory endothelial function (CFRe)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adenosine</strong></td>
<td>% Δ in ratio of hyperaemic to rest APV (i.e., CFR) &gt;2.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(microcirculation)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acetylcholine</strong></td>
<td>-</td>
<td>% Δ in coronary artery diameter &gt;20%</td>
<td>% Δ in CBF &gt;50%</td>
</tr>
<tr>
<td>(epicardial and microcirculation)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NTG</strong> (epicardial)</td>
<td>% Δ in coronary artery diameter QCA &gt;20%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Coronary blood flow (CBF) = 0.5 x velocity x area
Coronary blood flow (CBF) = 0.5 × APV × (radius² × π)

---

- Resting full-cycle ratio (RFR)
- Fractional flow reserve (FFR)
- Index of microvascular resistance (IMR)
- Coronary flow reserve (CFR) (Thermodilution)
Evenaars et al. Doppler flow velocity and thermodilution to assess coronary flow reserve: a head-to-head comparison with $^{15}$O-H$_2$O PET. JACC Interv 2018; 11: 2044-2054.

Risk of invasive coronary reactivity testing: low risk (1%) of adverse events

Safety of Coronary Reactivity Testing in Women With No Obstructive Coronary Artery Disease

Results from the NHLBI-Sponsored Wise (Women's Ischemia Syndrome Evaluation) Study

293 women, mean age 54 years (SD 10)

Results: CRT-SAEs occurred in 2 women (0.7%) during the procedure. 1 had coronary artery dissection, and 1 developed MI associated with coronary spasm. CRT-AEs occurred in 2 women (0.7%) and included 1 transient air microembolism and 1 deep venous thrombosis. There was no CRT-related mortality. In the mean follow-up period of 5.4 years, the MACE rate was 8.2%, including 5 deaths (1.7%), 8 nonfatal MIs (2.7%), 8 nonfatal strokes (2.7%), and 11 hospitalizations for heart failure (3.8%).

Conclusions In women undergoing CRT for suspected MCD, contemporary testing carries a relatively low risk compared with the MACE rate in these women. These results support the use of CRT by experienced operators for establishing definitive diagnosis and assessing prognosis in this at-risk population.

Wei J et al. JACC Cardiovasc Interv 2012;5:646–53 © 2012 by the American College of Cardiology Foundation

AllinaHealth® MINNEAPOLIS HEART INSTITUTE

16 studies, 12585 patients
Pooled estimate of incidence of major complications was 0.5% without any reports of death.

Safety of Provocative Testing With Intracoronary Acetylcholine and Implications for Standard Protocols

14 studies, 12585 patients
Pooled estimate of incidence of major complications was 0.5% without any reports of death.

Minor complications were noted in 3.5% of the patients with intracoronary acetylcholine.

AllinaHealth® MINNEAPOLIS HEART INSTITUTE

Although the overall incidence of major complications was 0.5%, the rate of major complications can vary depending on diagnostic criteria, ethnicity, and acetylcholine dose. These results help in standardizing the provocative protocol as well as a complication reporting system. ACM = acetylcholine, MI = myocardial infarction, VP = venous pooling, VD = venous dilatation, VVT = venous tissue pooling.
Case presentation

- 70 year-old female with a history of hypertension and dyslipidemia with dyspnea on exertion and chest discomfort.
- Previous CCTA ~3 years ago with no significant obstructive CAD, CAC 100.
- RHC: RA 11, PA 45/18 (30), PCWP 18, CO 5.8, CI 2.6
- LVEDP 17 mmHg
Putting it all together

- **Symptoms**
  - Reproduction of index symptoms

- **ECG**
  - Ischemic ECG findings

- **CFR (Adenosine)**
  - Normal CFR: 2.5 Doppler, 2.0 TD

- **CBF response (ACH)**
  - Normal % delta CBF>50% (Doppler)

- **Microvasculature**
  - TD → IMR ; Doppler → HMR

- **Epicardial coronary vasomotion (ACH/ NTG)**
  - Normal >20% diameter (dilation)
**ORIGINAL RESEARCH**

**IMPROVe-CED Trial: Intracoronary Autologous CD34+ Cell Therapy for Treatment of Coronary Endothelial Dysfunction in Patients With Angina and Nonobstructive Coronary Arteries**

Michel T. Corban, Tahami Tabrizi, Dina Nacos, Valerio Scardelli, Bradley R. Lewis, John Ko, Ryan Qadri.

**METHODS:** Twenty 64 patients with intracoronary autologous CD34+ cell (MACAS) 1000 cells/mL iv administration into the left anterior descending, intracoronary cell microinjection treatment in 2012. The primary endpoint was change in peak nocturnal coronary flow velocity (CFV) from baseline to 6 months. The secondary endpoints included changes in the Coronary Artery Disease (CAD) score, the Angina Quality of Life (AQoL) score, and the CCS Angina Class. CFV was measured using intracoronary Doppler flowmetry. CAD score was assessed using the Canadian Cardiovascular Society (CCS) angina classification system. AQoL was assessed using the Angina Quality of Life (AQoL) questionnaire. CCS Angina Class was assessed using the Canadian Cardiovascular Society (CCS) angina classification system. All patients were followed for 6 months.

**RESULTS:** The mean change in CFV at 6 months was 1.27 ± 1.10 cm/s (p=0.014) in the treatment group compared to the control group (mean change 0.15 ± 0.87 cm/s, p=0.19). At 6 months, the CCS Angina Class improved from 1.27 ± 1.10 cm/s to 1.15 ± 0.98 cm/s (p=0.05). The Angina Quality of Life (AQoL) score improved from 0.15 ± 0.18 to 0.13 ± 0.16 (p=0.005). The CCS Angina Class improved from 1.27 ± 1.10 cm/s to 1.15 ± 0.98 cm/s (p=0.005).

**CONCLUSIONS:** Intracoronary infusion of autologous CD34+ cells improved coronary flow velocity and reduced angina severity in patients with nonobstructive coronary artery disease. This suggests a potential role for autologous CD34+ cell therapy in the treatment of coronary artery disease.

**AllinaHealth® MINNEAPOLIS HEART INSTITUTE**

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**ORIGINAL ARTICLE**

**Autologous CD34+ Stem Cell Therapy Increases Coronary Flow Reserve and Reduces Angina in Patients With Coronary Microvascular Dysfunction**

Timothy J. Henry, MD, MD; Niall Barrie, MD; MD; Merit Wofford, MD; Michel T. Corban, MD; Glyndor Quadea, MD; Sandy Jun, MD; Zhou; Chi Liu; Liang Li; Jing Wang; MD; Michelle Lewis, BS; Ann M. Schmerberger, RN, MSN; CCS; Ronod, Lila; Barry; PhD; M genitals; Tung; Deng; Yihua; Qian; HS; Anna Lee, PhD; William K. Siekmeier, MD; PhD; Douglas WM; Losordo, MD; Anne Lerner, MD; ND

**METHODS:** In a prospective, randomized, controlled trial, 90 patients with chronic, stable angina and coronary microvascular dysfunction were randomized to receive autologous CD34+ stem cell therapy (n=45) or placebo (n=45). The primary endpoint was change in coronary flow reserve (CFR) from baseline to 6 months. The secondary endpoints included change in CCS angina class, change in Angina Quality of Life (AQoL) score, and change in 6-minute walk distance. The trial was conducted at the Minneapolis Heart Institute Foundation, Minneapolis, MN.

**RESULTS:** The mean change in CFR at 6 months was 1.27 ± 0.87 cm/s (p=0.008) in the treatment group compared to the control group (mean change 0.15 ± 0.87 cm/s, p=0.19). At 6 months, the CCS Angina Class improved from 1.27 ± 1.10 cm/s to 1.15 ± 0.98 cm/s (p=0.05). The Angina Quality of Life (AQoL) score improved from 0.15 ± 0.18 to 0.13 ± 0.16 (p=0.005). The CCS Angina Class improved from 1.27 ± 1.10 cm/s to 1.15 ± 0.98 cm/s (p=0.005).

**CONCLUSIONS:** Intracoronary infusion of autologous CD34+ cells improved coronary flow velocity and reduced angina severity in patients with nonobstructive coronary artery disease. This suggests a potential role for autologous CD34+ cell therapy in the treatment of coronary artery disease.
DISCOVER INOCA (NCT05288361): **500 participants** over 2-years at 10 US sites

**DISCOVER INOCA**: adult patients >18 years of age with suspected ischemic heart disease referred to undergo clinically indicated invasive coronary angiography, with no obstructive CAD (angiographically normal, <50% CAD, or ≥50 but <70% with FFR>0.81 or RFR>0.90

**Diagnostic assessment**: coronary angiography, acetylcholine provocation, coronary physiology, intra-coronary imaging.

**Patient reported outcomes**: SAQ, EQ-5D-5L, PHQ-8, GAD-7

**Study follow-up**: 30-days, 6-months, 12-months, annually for 5-years.

**Primary endpoint**: major adverse cardiovascular events (MACE) defined as a composite of cardiovascular death, myocardial infarction, hospitalization for cardiovascular causes, or coronary revascularization at a follow-up of 5-years.

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**Take home points**

- Microvascular disease is common and nomenclature is evolving with terms such as INOCA and MINOCA used to refer to patients with stable and unstable presentations.
- MVD represents a spectrum of those with epicardial coronary spasm to those with abnormal microcirculation without spasm.
- Non-invasive MBF can be assessed using PET or CMRI.
- The gold-standard comprehensive approach remains invasive evaluation, which can be performed using either Doppler or Thermodilution with ACH spasm provocation.
- Randomized data emerging to support diagnosis and tailored therapies.
Yader Sandoval, MD, FACC, FSCAI
Interventional Section, Minneapolis Heart Institute, Abbott Northwestern Hospital, Minneapolis, MN
Center for Coronary Artery Disease (CCAD), Minneapolis Heart Institute Foundation, Minneapolis, MN
Adjunct Associate Professor of Medicine, Mayo Clinic College of Medicine and Science

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