MHIF FEATURED STUDY: KPL-301-C203

DESCRIPTION:
Phase 2/3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of single IV dose of mavrilimumab in adult subjects hospitalized with severe COVID-19 pneumonia and hyper-inflammation to reduce progression to respiratory failure or death. Mavrilimumab targets the GM-CSF receptor, neutralizing overexpression of GM-CSF associated with inflammation. This may address severe cytokine storm syndrome seen in subjects with COVID-19 and the immediate need to reduce rising mortality.

CONDITION:
Severe COVID-19 pneumonia and hyper-inflammation

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SPONSOR:
Kiniksa

OPEN AND ENROLLING:
EPIC message: Research MHIF Patient Referral

CRITERIA LIST/QUALIFICATIONS:

Inclusion:
• >18 years old
• Positive SARS-CoV-2 within 14 days
• Bilateral pneumonia on chest x-ray or CT
• Elevated ferritin, CRP, D-dimer, LDH, or history of fever <7 days
• Requiring non-invasive ventilation or oxygen supplementation to maintain SpO2 >92% (i.e. nasal cannula, face mask, BiPAP, CPAP) or invasive ventilation <48 hours

Exclusion:
• Onset of COVID-19 symptoms >14 days
• Hospitalized for SARS-CoV-2 >7 days
• Prior severe or concomitant illness (i.e. pulmonary alveolar proteinosis, severe and uncontrolled pulmonary disease other than COVID-19 pneumonia, pre-existing LVEF <35%, MI/stroke/hemodynamic instability/cardiogenic or septic shock <30 days, concomitant uncontrolled systemic or bacterial infection)
• Recent cell-depleting biological therapies or immunosuppressants (except corticosteroids)
• Received hydroxychloroquine within last 3 months

EXCLUSION:
• Onset of COVID-19 symptoms >14 days
• Hospitalized for SARS-CoV-2 >7 days
• Prior severe or concomitant illness (i.e. pulmonary alveolar proteinosis, severe and uncontrolled pulmonary disease other than COVID-19 pneumonia, pre-existing LVEF <35%, MI/stroke/hemodynamic instability/cardiogenic or septic shock <30 days, concomitant uncontrolled systemic or bacterial infection)
• Recent cell-depleting biological therapies or immunosuppressants (except corticosteroids)
• Received hydroxychloroquine within last 3 months
CT imaging of coronary artery plaque: Substrate-based approach to coronary artery disease

Victor Cheng, MD
Cardiac Imaging
Disclosures

• None
Outline

• Coronary CTA: Stenosis paradigm
• Thin-cap fibroatheroma (TCFA, “tik-fa”)
• CTA imaging of TCFA features and risk
• Real-life measurement of CTA plaque findings
• Application of plaque characterization
• Uncertainties
What did it show?

How do the coronaries look?

Is the patient safe for discharge?

Anything interesting on the CT?

Good morning!

What did it show?

Will invasive angiography of my patient show obstructive, culprit disease?
You already know…

• Current use of coronary CTA is dominated by the “stenosis model”

• “Cath-lite”: Accurate compared to invasive gold standard (>100 comparative studies including ACCURACY 2008, Meta-analysis BMJ 2019, VERDICT 2020)

• Absence of >50% diameter stenosis…
  • Excludes epicardial CAD as cause of outpatient symptoms
  • Safely excludes ACS in intermediate-probability symptomatic patients in the ED and in the hospital
  • Excludes stenotic CAD before noncoronary cardiac surgery
  • Excludes CAD as cause of cardiomyopathy
CTA stenosis paradigm works

- Stenosis threshold of >50% on coronary CTA identifies patients at very low probability for ACS, and expedites discharge (CT-STAT 2011, ACRIN-PA 2012, ROMICAT II 2012)
- CTA-based outpatient management is at least as safe as functional testing-based management (PROMISE 2015, SCOT-HEART 2015)
- CTA dependably excludes obstructive disease in the left main coronary artery in patients with significant inducible ischemia (ISCHEMIA 2020)
CTA stenosis paradigm works

Current Evidence and Recommendations for Coronary CTA First in Evaluation of Stable Coronary Artery Disease

Michael Poon, MD, a John R. Lesser, MD, b Cathleen Biga, MSN, RN, c Ron Blankstein, MD, d,e Christopher M. Kramer, MD, f James K. Min, MD, g,h Pamela S. Noack, PhD, MBA, a Christina Farrow, i Udo Hoffman, MD, MPH, j Jaime Murillo, MD, k Koen Nieman, MD, PhD, l,m Leslee J. Shaw, PhD n

RECOMMENDATIONS

To move forward toward a coronary CTA-first paradigm, this ACC Summit Team recommends the following:

CTA stenosis paradigm ignores lots of patients

Nonobstructive plaque greatly outnumber obstructive plaque

Nonobstructive plaques develop into the majority of future culprit lesions that cause myocardial infarctions

Figure 2 (A) Severity of coronary stenosis and 5-year risk of coronary occlusion (open bars) or myocardial infarction (closed bars). Data from Van Lierde et al.\(^3\) (B) Stenosis severity of culprit atherosclerotic plaque causing myocardial infarction.

Newby D. Heart. 2010;96.
Nonobstructive plaque and events

Can Coronary Angiography Predict the Site of a Subsequent Myocardial Infarction in Patients With Mild-to-Moderate Coronary Artery Disease?

William C. Little, MD, Martin Constantinescu, MD, Robert J. Applegate, MD, Michael A. Kutcher, MD, Mark T. Burrows, PA, Frederic R. Kahl, MD, and William P. Santamore, PhD

42 consecutive patients with MI
Had cath prior to and within 30 days after MI
Range from 4 days to 6.3 years before MI
Stenosis severity did not predict culprit location

Nonobstructive plaque and events

PROSPECT cohort study
697 patients with ACS underwent 3 vessel IVUS during cath
Followed for median 3.4 years: Cardiac death, cardiac arrest, MI, angina hospitalization
Events occurred in 13% of index culprit plaques and 12% of nonculprit plaques
Mean diameter stenosis % of event-causing 106 nonculprit plaques: 32% index, 65% at event

Nonobstructive plaque and events

- CONFIRM Registry
- 23854 patients
- 12 centers, 6 countries
- Median follow-up 2.1 yr
- 404 all-cause deaths
- 8114 with nonobstructive atherosclerosis, 5594 total for 1V+2V+ 3V

Patients with nonobstructive plaque died as often as patients with 1 artery obstructive disease

Nonobstructive plaque and events

- Much higher event rate when CT finds 4+ segments with nonobstructive plaque (median follow-up 3.6 years)

Figure 1. A, Rate of cardiovascular death or myocardial infarction according to the presence, severity, and extent of coronary artery disease (CAD). There is a significant difference ($P<0.01$) in rates for all comparisons except nonobstructive CAD with segment involvement score (SIS) $>4$ and obstructive CAD with SIS $\leq 4$. B, Rate of major cardiovascular events. C, Rate of all-cause death. Log-rank $P<0.01$ for all graphs.

Nonobstructive plaque and events

PROMISE

- Strategy trial
- 4500 CTA, 4600 Functional test
- Followed for median 26 months
  - All cause death
  - CV death
  - Myocardial infarction
  - Unstable angina

In CTA arm, 77% of CV deaths and MI occurred in patients with nonobstructive disease on CTA

In functional testing arm, 67% of events in patients with normal results

Nonobstructive plaque and events

Before a coronary event, patients can produce normal results on functional testing, but their coronary arteries almost always show plaque on CTA.

*CTA is the only noninvasive modality that can find the eventual “culprit” nonobstructive plaque.*
Coronary CTA finds nonobstructive plaque

• Basic plaque categorization

Calcium scans only see calcified plaques and calcified parts of partially calcified plaques
Nonobstructive plaque: Incredibly prevalent

- 30154 men and women 50-64 yo
- None with history of coronary event
- 25000 had coronary CTA
- Atherosclerosis in 42% of population
- Extensive atherosclerosis (≥4 segments) in 13%
- Potentially obstructive disease in 5%

So much nonobstructive plaque! Isn’t looking for the bad actors hopeless?
Culprit plaques

THIN-CAP FIBROATHEROMA “TCFA”

Thin-cap fibroatheroma (TCFA)

Cap rupture or erosion → Thrombus → Stenosis

ACUTE CORONARY EVENT

TCFA in PROSPECT

Oooh. That plaque is kind of big...

Whoa!

Nasty!
TCFA features

Features of Ruptured/Rupture-Prone Plaques

**MORPHOLOGY**
- Large necrotic core
- Fibrous cap covering the necrotic core
- Thin (thickness usually <65 μm)
- High macrophage density
- Few smooth muscle cells
- Expansive remodeling preserving the lumen
- Neovascularization from vasa vasorum
- Plaque hemorrhage
- Adventitial/perivascular inflammation
- Spotty calcification

**INFLAMMATION**
*The same features, except cap rupture and luminal thrombus, are assumed to characterize vulnerable plaques of the rupture-prone type.*

29.8 HU

Low attenuation

D1/D2 > 1.1

Positive remodeling

Spotty calcification

Large necrotic core
- Fibrous cap covering the necrotic core
  - Thin (thickness usually < 65 μm)
  - High macrophage density
  - Few smooth muscle cells

Expansive remodeling preserving the lumen
- Neovascularization from vasa vasorum
- Plaque hemorrhage
- Adventitial/perivascular inflammation
- Spotty calcification

Can CTA find TCFA?

“Napkin-Ring” Sign

“Napkin-Ring” is a specific pattern of low attenuation + positive remodeling

Can CTA find TCFA?

Comparisons to histology, virtual histology IVUS, and OCT:
Low sensitivity, Good specificity.
**CTA misses many TCFA.**
When multiple features on CT suggest TCFA, it’s probably right.

CTA imaging of TCFA features and risk:

*Hold on to your voxels*

**Low attenuation (LA)**

- 29.8 HU

**Positive remodeling (PR)**

- D1/D2 > 1.1

**Spotty Calcification (SC)**

**NAPKIN-RING SIGN (NRS)**

- Large necrotic core
- Fibrous cap covering the necrotic core
  - Thin (thickness usually < 65 μm)
  - High macrophage density
  - Few smooth muscle cells
- Expansive remodeling preserving the lumen
- Neovascularization from vasa vasorum
- Plaque hemorrhage
- Adventitial/perivascular inflammation
- Spotty calcification
Looking for TCFA on CTA

- 1059 consecutive patients with CTA at enrollment
- Manually determined positive remodeling (PR), low attenuation (LA), and spotty calcification (SC)
- Mean 27 months follow-up for subsequent ACS
- 45 patients showed PR and LA, 10 (22%) had ACS
- 820 patients showed neither, 4 (0.5%) had ACS
- **PR and LA classified as high-risk features (SC demoted), especially in the “2-feature” plaque**

TCFA features on CTA

- 3158 patients
- High-risk plaque = PR + LA
- Included obstructive disease as predictor
- Mean 4 years follow-up

- Non high-risk plaque & nonobstructive: 1.2% with ACS
- High-risk plaque & obstructive: 19%
- High-risk plaque & nonobstructive: 15%

TCFA features on CTA

- 449 patients had a second CTA for clinical reasons
- 56 had plaque progression = ↑ in stenosis grade or ↑ in positive remodeling ratio
- Plaque progression was a strong, independent predictor of ACS

Plaque Progression

Proximal and mid LAD

Time interval: 2 years
Rapid plaque progression is not new

- 20 patients with cath within 1 week before AMI
- 20 patients with cath within 6-18 months before AMI
- Eventual culprit lesion appeared substantially more stenotic days before AMI

High-risk plaque: SCOT-HEART

- 1769 patients with baseline CTA
- Followed for 5 years
- Plaque with PR or LA = high-risk plaque (HRP, less strict than Motoyama)
- Nonobstructive HRP: 3 x risk of coronary death or MI
- Nonobstructive with HRP: similar coronary event rate as obstructive without HRP
- Obstructive HRP: 10 x risk!

High-risk plaque: SCOT-HEART

- Specific analysis of low attenuation (LA) plaque burden, as % of artery volume
- LA plaque burden >4% showed 5x higher incidence of AMI
- LA burden is stronger than ASSIGN clinical risk score, calcium score, and presence of obstructive disease

High-risk plaque: PROMISE

- 4415 patients in the CTA strategy arm analyzed
- Median 25 m follow-up for death, MI, UA
- 676 with PR, LA, or NRS (less strict than Motoyama)
- Total 131 events, 86 (66%) in patients with nonobstructive CAD
  - 4.8% in 505 with HRP
  - 2.9% in 2109 without HRP
- HRP was associated with 6 fold risk (4.8% to 0.8%) in women < 60 years old
- HRP was not predictive in patients with obstructive CAD

Hold on…

All of these high-risk features depend on having a pretty large noncalcified plaque, and CTA can’t see smaller TCFAs.

Wouldn’t this suggest having lots of noncalcified plaque without high risk features still increases chances of having TCFAs and increases risk?
**High-risk plaque and ACS: ICONIC**

- Multinational CTA registry
- 3 year follow-up

- Nested case control using *propensity matching* of 234 patients with ACS after index CTA to 234 without ACS
  
  Matching by:
  
  *risk factors*  
  *CAD severity*

High-risk plaque and ACS: ICONIC

- 65% of patients with ACS had nonobstructive disease on CTA
- Patients with ACS had higher amounts of...
  - Low attenuation (necrotic core)
  - “fibrofatty” plaque
  - Total noncalcified plaque
  - Positive remodeling
  - Spotty calcification

*Total noncalcified plaque volume was associated with risk*

High-risk plaque progression: PARADIGM

- Multinational study
- 1255 consecutive patients with diagnostic quality serial coronary CTA ≥2 years apart
- All arterial segments ≥2 mm quantified for plaque
- Comparisons made between patients taking and not taking statins

High-risk plaque progression: PARADIGM

Statin therapy is associated with reduced total plaque formation, reduced noncalcified plaque formation, and increased calcified plaque formation

High-risk plaque progression: PARADIGM

- Statin therapy was associated with
  
  Reduced progression in ALL COMPONENTS of noncalcified plaque

  Reduced development of high-risk plaque features

<table>
<thead>
<tr>
<th>TABLE 3 Effects of Statins on Atherosclerosis</th>
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<tr>
<td>Hazard Ratio of Statin</td>
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<tr>
<td>Newly developed diameter stenosis ≥50%</td>
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<tr>
<td>Annualized progression of atherosclerosis (% per yr) to above median</td>
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<tr>
<td>Total PAV</td>
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<tr>
<td>Calcified PAV</td>
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<tr>
<td>Noncalcified PAV*</td>
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<td>Fibrous PAV</td>
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<td>Fibro-fatty PAV</td>
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<td>Low-attenuation PAV</td>
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<td>Newly developed adverse atherosclerotic features</td>
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<td>High-risk plaque†</td>
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<tr>
<td>Positive arterial remodeling</td>
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<tr>
<td>Low-attenuation plaque</td>
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<tr>
<td>Spotty calcification</td>
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</table>

Summary: TCFA features on CTA

• CTA Noninvasively identifies some TCFA features
  • *Low attenuation, Positive remodeling, Napkin-ring sign*

• TCFA features predict increased coronary event risk, independent of obstruction

• Higher noncalcified plaque volume predicts higher event risk and likely represents amount of plaque capable of becoming high-risk

• Plaque progression is a strong predictor of coronary risk risk

• Statin therapy slows progression of TCFA features
Real-life measurement of CTA plaque findings
Measuring CTA plaque

• Referenced studies manually combed CTA to detect plaque features and measure plaque volume
  Extremely time consuming and not feasible for clinical work!

• Visual detection of positive remodeling and low attenuation has limited reproducibility and is at risk of missing findings
Automatic plaque tracing: SCOT-HEART

- Specific analysis of low attenuation plaque burden, as % of artery volume
- Low attenuation plaque burden >4% showed 5x higher incidence of AMI
- Low attenuation burden is stronger than ASSIGN risk score, calcium score, and presence of obstructive disease

Automatic plaque tracing

User sets a few boundaries; IVUS validated measurements of plaque features

 Courtesy Dr. Damini Dey, Cedars-Sinai Medical Center
Automated plaque tracing

Extracted RCA, contoured lumen walls, and detected all plaques

NO USER INTERFACE NEEDED

Courtesy Dr. James Min, Cleerly
Automated plaque tracing

Quantification and characterization of plaque

Courtesy Dr. James Min, Cleerly
Step 4 – For the Patient
Interactive Image-Based Prevention

Communicate Science. Simply.

Quantitative Disease Tracking Over Time

Risk of Heart Attack

Risk of Rapid Progression

Response to Medications

Courtesy Dr. James Min, Cleerly
CT plaque radiomics

Radiomics is the process of extracting a large number of quantitative features from medical images to create big data in which each abnormality is characterized by hundreds of parameters indiscernible to the human eye. Computational techniques such as data mining and machine learning can then be used to identify new imaging patterns or biomarkers that associate with clinical features or outcomes. In cardiac magnetic...
CT plaque radiomics

- Expert readers identified 30 plaques with NRS and matched to 30 plaques with similar compositions and no napkin ring.
- Radiomics-based analysis identified **418 features of difference** between the NRS and non-NRS plaques!

That’s nice.

But really, isn’t therapy just aspirin and statins?
Targeting CAD therapeutics

**ODYSSEY OUTCOMES**
- Alirocumab binds to PCSK9 protein to inhibit its action in blocking bloodstream LDL removal
- Alirocumab + high dose statin vs placebo + high dose statin in 18924 patients after ACS
- LDL lowered to 50 mg/dL, **NNT 49 over 4 years to prevent 1 ACS / stroke / cardiac death**

Targeting CAD therapeutics

**COMPASS trial**

- 27395 stable patients with documented CAD, PAD, or both
- Aspirin + 2.5 mg daily rivaroxaban vs aspirin + placebo
- Median follow-up 23 months

- NNT = 74 over 2 years to prevent 1 MI / stroke / CV death
- NNH = 80 over 2 years to cause 1 additional major bleeding episode

Targeting CAD therapeutics

**COLCOT trial**
- 4745 patients within 30 days of MI
- Colchicine 0.5 mg daily vs placebo
- Median follow-up 22.6 months

- **NNT = 59 over 2 years to prevent** 1 MI / ACS / stroke / CV death
- **NNH = 189 over 2 years to cause 1 additional episode of pneumonia**

Targeting CAD therapeutics

LoDoCo2 trial
- 5522 stable patients with CAD on cath, CTA, or CCS≥400
- Colchicine 0.5 mg daily vs placebo
- Median follow-up 28.6 months
- NNT = 40 over 3 years to prevent 1 MI / ACS / stroke / CV death
- Trend of increased non-CV death in colchicine group; NNH = 167

Targeting therapeutics

• Trial populations look similar in risk by conventional means

• But the underlying coronary plaque substrate was not specified and likely quite variable, meaning the risk level in these populations is actually highly variable

• This variability dilutes treatment benefit, making it difficult to produce compelling benefit/risk ratios

• CTA imaging of coronary artery plaque substrate can select a more consistent high risk population…
  • Higher treatment effect, demonstrable in a smaller population
Targeting therapeutics

Patient 1:
Proximal LAD stent, 1 calcified plaque in proximal RCA

Aspirin
Instense statin

Patient 2:
Proximal LAD stent, nonobstructive noncalcified plaques in LAD, LCX, and RCA, 1 plaque shows napkin ring, 2 show positive remodeling

Aspirin
Colchicine
Intense statin
PCSK9 antibody
Targeting therapeutics

Patient 2, 2 years later:
Mild increase total plaque volume, substantial reduction in noncalcified plaque, disappearance of napkin ring and positive remodeling

Aspirin  Colchicine
Intense statin
PCSK9 antibody

Patient 2, 2 years later:
Total plaque volume and noncalcified plaque volume increased by 25%, 2 more lesions with positive remodeling

Aspirin  Colchicine
Intense statin  Inclisiran
PCSK9 antibody  Rivaroxaban
Plaque quantification in trial form

**EVAPORATE trial**
- REDUCE-IT showed icosapent ethyl (Vascepa) lowered TG and reduced cardiovascular death and MI
- 80 stable patients with coronary atherosclerosis by cath or CTA, high fasting TG, and on statin
- Icosapent ethyl 2g bid vs placebo
- Sequential CTA at baseline, 9 months, and 18 months
- **All components of noncalcified plaque decreased with treatment**

NANOPARTICLES are coming...
Uncertainties
Uncertainties…

There are many! Some smaller scale questions …

• What are the best cut-offs for low attenuation plaque burden, positive remodeling, and noncalcified plaque volume burden?

• What is the optimal time for serial scanning to identify rapid progressors? What is the true clinical utility of monitoring plaque change?

• Does plaque characterization matter at all in patients with bypass grafts?

• Should CTA be done routinely after an acute coronary event to identify at risk plaque (“virtual” PROSPECT)?
Uncertainties…

Some are bigger picture…

• If we use plaque characterization, shouldn’t we change the definition of “coronary artery disease” to be less dependent on the presence of obstruction?

• Are we ready to quantify risk using direct plaque imaging instead of nonimaging surrogate algorithms (ASCVD calculator)?
Whose high-risk plaque gets noticed?

- Acute coronary event
- Cardiac symptoms / abnormality
- Noncardiac symptoms
- No symptoms & No history

Should we also image asymptomatic people?
Conclusions

• The stenosis paradigm for coronary artery disease does not address the substrate of nonobstructive TCFA, which causes the majority of acute coronary events.

• Coronary CTA is the one noninvasive test that can be safely used in large populations AND routinely provide information about nonobstructive plaque.

• Cohort studies have consistently shown CTA capable of finding TCFA features that dramatically increase the risk of acute coronary events.
Conclusions

• Software solutions that detect and measure high risk plaque features are going live, and we need to figure out how to use the information to improve patient care.

• CTA characterization of coronary artery plaque is positioned to help find the highest risk individuals…
  • *Enhance treatment trial patient selection*
  • *Drive customization of matching patients to treatments*
Thank you!

Stay safe

Happy Thanksgiving!
CT imaging of coronary artery plaque: 
*Substrate-based approach to coronary artery disease*

Victor Cheng, MD
Cardiac Imaging
Plaque Progression

Proximal LCX

Time interval: 26 months
Proximal RCA
Singular LAD Proximal +LA +PR
### 6-week diagnosis

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<td>402 (19%)*</td>
<td>52 (3%)</td>
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<td>899 (43%)</td>
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<td>1 (0%)</td>
<td>265 (13%)*</td>
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<td>593 (29%)</td>
<td>1062 (51%)</td>
<td>272 (13%)</td>
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1 in 5 had diagnosis impression changed after CTA

<1% had diagnosis impression changed

SCOT-HEART. Lancet 2015; 385.
Plaque metabolic imaging:

CTA + PET
Plaque Metabolism

• 2 agents

$^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG): Inflammation

$^{18}$F-sodium fluoride ($^{18}$F-NaF): intraplaque calcium turnover
18F-FDG plaque imaging

12 of 20 s/p AMI with target-background signal ratio (TBR) > 2

1 of 7 with TBR > 2

18F-FDG plaque imaging

12 weeks atorvastatin 20-80 mg

18F-FDG plaque imaging

NO MOMENTUM! Imaging was too complex.

Low-carbohydrate, high fat preparation dinner.
Then fast through scan

18F-NaF plaque imaging

- Microscopic calcium turnover is a marker of plaque formation and plaque inflammatory activity
- 18F-NaF binds with exposed hydroxyapatite crystals on bony surfaces and vascular calcifications
- In vascular system, intensity of signal is related to surface area of hydroxyapatite

18F-NaF plaque imaging

Predictors of 18F-sodium fluoride uptake in patients with stable coronary artery disease and adverse plaque features on computed tomography angiography

Jacek Kwiecinski¹,², Damini Dey¹, Sebastien Cadet¹, Sang-Eun Lee¹, Balaji Tamarappoo¹, Yuka Otake¹, Phi T. Huynh¹, John D. Friedman¹, Mark R. Dweck¹, David E. Newby ³, Mijin Yun¹, Hyuk-Jae Chang³, Piotr J. Slomka¹¹, and Daniel S. Berman³

55 patients with CTA showing 3 of: low attenuation, positive remodeling, spotty calcification, >50% stenosis, plaque volume >100 mm³

18F-NaF uptake most associated with low attenuation

18F-NaF plaque imaging

CTA and 18F-NaF PET done on separate days

1 hour versus 3 hour post-injection imaging

Metabolic plaque imaging...

- Complex imaging protocols
- Requires expertise in CTA and PET
- Costly
- Still investigational
- Lacks outcome information

Pathway to clinical application still unclear
Targeting CAD therapeutics

**ORION-10** and **ORION-11**

- Injectable inclisiran is an interfering RNA molecule that inhibits hepatic PCSK9 protein production
- O-10 Inclisiran vs placebo in 1561 patients, 68% on high intensity statin
- O-11 Inclisiran vs placebo in 1617 patients, 79% on high intensity statin
- Inclisiran lowered LDL by 50%

Wait… show the graph again

? Some more subtle high-risk features missed
? Plaque progression

Nonobstructive, no HRP caught up!