The lipid rich plaque study – a glimpse to the results

Professor Carlo Di Mario, MD, PhD. FACC, FESC
University of Florence, Italy

Presentation based on available data presented at CRT 2018 by:

Ron Waksman, MD, PI LRP Study
Professor of Medicine, (Cardiology) Georgetown University
Director, Cardiovascular Research Advanced Education,
MedStar Heart & Vascular Institute, Washington DC
COLOR Registry

Patients with Clinical Indication for Coronary Angiography and Possible Revascularization

N=1899

NIRS only  n=705
NIRS/IVUS  n=1194

Excluded:
No NIRS or poor quality  n=185
Planned CABG  n=7

Pre-PCI Culprit NIRS (1265 lesions in 1168 pts)

Non-culprit NIRS (1072 lesions in 927 pts)

Median Follow-up 731d (IQR 711, 746)

Primary Endpoint
MACE (cardiac death, myocardial infarction, stent thrombosis, revascularization, hospitalization)

ClinicalTrials.gov NCT00831116
# COLOR Registry

## Patient Characteristics

N=1899

### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n=1899</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>63.7±10.7</td>
</tr>
<tr>
<td>Female/Male</td>
<td>24.7% / 75.3%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>89.9%</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>38.2%</td>
</tr>
<tr>
<td>- IDDM</td>
<td>5.9%</td>
</tr>
<tr>
<td>- NIDDM</td>
<td>32.3%</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>90.4%</td>
</tr>
<tr>
<td>Current Smoking</td>
<td>20.7%</td>
</tr>
<tr>
<td>PVD</td>
<td>9.9%</td>
</tr>
<tr>
<td>Family Hx</td>
<td>55.2%</td>
</tr>
<tr>
<td>Prior MI</td>
<td>29.7%</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>51.3%</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>8.9%</td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
</tr>
<tr>
<td>- Total cholesterol</td>
<td>154.5 ± 43.8</td>
</tr>
<tr>
<td>- LDL</td>
<td>86.2 ± 35.7</td>
</tr>
<tr>
<td>- HDL</td>
<td>40.6 ± 12.9</td>
</tr>
<tr>
<td>- TG</td>
<td>141.6 ± 105.4</td>
</tr>
</tbody>
</table>

### Clinical Presentation

<table>
<thead>
<tr>
<th>Type</th>
<th>n=1899</th>
</tr>
</thead>
<tbody>
<tr>
<td>- STEMI</td>
<td>1.7%</td>
</tr>
<tr>
<td>- Non-STEMI</td>
<td>9.3%</td>
</tr>
<tr>
<td>- Unstable angina</td>
<td>49.3%</td>
</tr>
<tr>
<td>- Stable angina</td>
<td>39.7%</td>
</tr>
</tbody>
</table>

### Medical Therapy

<table>
<thead>
<tr>
<th>Therapy</th>
<th>n=1899</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>96.6%</td>
</tr>
<tr>
<td>ADP receptor antagonist</td>
<td></td>
</tr>
<tr>
<td>- Plavix</td>
<td>76.7%</td>
</tr>
<tr>
<td>- Prasugrel or Ticagrelor</td>
<td>12.2%</td>
</tr>
<tr>
<td>Statin</td>
<td>91.3%</td>
</tr>
</tbody>
</table>
2-Year Outcomes

Number at risk:

<table>
<thead>
<tr>
<th>Category</th>
<th>All</th>
<th>CL related</th>
<th>NCL related</th>
<th>Indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1,899</td>
<td>1,899</td>
<td>1,899</td>
<td>1,899</td>
</tr>
<tr>
<td>180</td>
<td>1,716</td>
<td>1,766</td>
<td>1,759</td>
<td>1,810</td>
</tr>
<tr>
<td>365</td>
<td>1,578</td>
<td>1,651</td>
<td>1,630</td>
<td>1,714</td>
</tr>
<tr>
<td>550</td>
<td>1,488</td>
<td>1,571</td>
<td>1,542</td>
<td>1,645</td>
</tr>
<tr>
<td>730</td>
<td>911</td>
<td>977</td>
<td>943</td>
<td>1,019</td>
</tr>
</tbody>
</table>

MACE (%)

- All patients
  - 0 days: 6.5%
  - 180 days: 9.7%
  - 365 days: 12.0%
  - 550 days: 14.1%
  - 730 days: 8.3%
- Non-culprit lesion
  - 0 days: 2.9%
  - 180 days: 4.2%
  - 365 days: 5.4%
  - 550 days: 6.0%
- Culprit lesion
  - 0 days: 3.1%
  - 180 days: 5.2%
  - 365 days: 6.7%
  - 550 days: 8.3%
- Indeterminate
  - 0 days: 1.1%
  - 180 days: 1.6%
  - 365 days: 2.0%
  - 550 days: 2.4%

Time in Days

- MACE (%): 0, 3, 6, 9, 12, 15
- Time in Days: 0, 180, 365, 550, 730
No Improvement of Non-culprit related Events

Enrollment completed in 2006 (n=697)

Enrollment completed in 2014 (n=1899)
**COLOR Registry**

**Culprit lesion related MACE by maxLCBI$_{4mm}$**

Number at risk:
- $< 304$: 632, 605, 584, 571, 544, 524, 521, 514, 313
- $\geq 304$: 633, 606, 600, 584, 571, 538, 532, 531, 356

Hazard Ratio = 0.83 [0.52, 1.30]  
P-Value = 0.41
Relationship Between NIRS and Culprit-lesion related MACE

maxLCBI\textsubscript{4mm}

- AUC [95% CI] = 0.53 [0.46, 0.60]
- P value = 0.42

Total lesion LCBI

- AUC [95% CI] = 0.53 [0.46, 0.60]
- P value = 0.41
Conclusions

1. In the present large-scale registry, non-culprit lesion-related events were more common than culprit-lesion-related post-PCI events during 2-year follow-up.

2. PCI of NIRS-defined LRPss (culprit lesion) was safe, and was not associated with increased peri-procedural or late adverse outcomes compared to PCI of non-LRPs.

3. The Clinical significance of NIRS-defined non-culprit LRPss will be determined by two ongoing prospective outcome studies (LRP study and PROSPECT-II).
Combination NIRS-IVUS Instrument

TVC Imaging System™
- Laser
- Computer with algorithms
- Pull-back and rotation device

TVC Insight™ Catheter
- Single use, 3.2 Fr
- Dual modality
- Spectroscopy – lipid core plaque
- IVUS – plaque structure
THE LIPID - RICH PLAQUE STUDY
Prospective Identification and Treatment of the Vulnerable Patient & the Vulnerable Plaque

9,000 PCI patients imaging 2+ vessels
- Cardiac death
- Cardiac arrest
- MI, ACS
- Revascularization
- Re-hospitalization for progressive angina

1562 patients

3,000 patients maxLCBI_{4mm} > 250 100% follow-up

6,000 patients maxLCBI_{4mm} ≤ 250 50% follow-up

2 year follow-up
THE LIPID - RICH PLAQUE STUDY

Active Sites and Research Staff

Washington Hospital Center: Dr. Waksman, J. Lancaster
Crittenton Hospital: Dr. Kazziha, M. Cribbs
St. John Hospital, Detroit: Dr. Lalonde, T. Jacobson
Charleston Area Medical Center: Dr. Lewis, J. Hogan
Columbia University Medical Center: Dr. Ali, L. Jaquez
Central Baptist Hospital: Dr. Skinner, J. Chapman
St. John’s Hospital, Springfield: Dr. Goswami, S. Smith, J. Davis
Emory University Hospital: Dr. Samady, E. Rasoul-Arzrumly
Methodist Hospital: Dr. Artis, K. Armstrong
Medical University of South Carolina: Dr. Powers, L. Carson
Community Heart and Vascular Hospital: Dr. Dube, J. Greene-Nashold
St. Luke’s Hospital: Dr. Walton, G. DeFreitas
Davis Medical Center: Dr. Kim, E. Mansell
McLaren Macomb Hospital: Dr. Zaina, T. Gardner-Mosley
Palm Beach Gardens Medical Center: Dr. Villa, E. Wettermann
University of Minnesota Medical Center: Raveendran, E. Caldwell
Amsterdam Medical Center: Dr. Wykrzykowska, R. Kraak
McLaren Bay Region: Dr. Lee, C. Quart
Alexian Brothers Heart & Vascular Institute: Dr. Pop, E. Enger
Northshore-LIJ Health System: Dr. Singh, P. Chu, G. Chan, M. Hyland
Florida Hospital Orlando: Dr. Arias, K. Mink
Latvian Centre of Cardiology: Dr. Erglis, S. Jegere
University of California Los Angeles Medical Center: Dr. Tobis, L. Douangvila
ACRC Cardiology/JFK Medical Center: Dr. Lovitz, J. Mitten
Hillcrest Oklahoma Heart Institute: Dr. Leimbach, J. Durham
Palmetto General Hospital: Dr. Diaz, R. Perez
Delray Medical Center: Dr. Carida, P. Bech
Emory Midtown: Dr. Liberman, T. Sanders
Royal Brompton Hospital: Dr. Di Mario, D. Dempster
New York Presbyterian Hospital – Cornell: Dr. Wong, H. Piscittell
University of Texas Galveston: Dr. Fujise, S. Ronald
Radboud University Medical Centre: Dr. ten Cate, I. Vereussel
SUSCH, Slovakia: Dr. Hudec, Zeleznikova
Maasstad Ziekenhuis: Dr. van der Ent, C. van Vliet
Erasmus Medical Center: Dr. Regar, E. Huijskens
University of Edinburgh: Dr. Newby, L. Flint
Metrohealth Hospital: Dr. Hodgson, J. Nichols
Memorial West: Dr. Tami, M. Abdurrahman
Heart Hospital Plano: Dr. Potluri, J. McCracken
Golden Jubilee National Hospital: Dr. McEntegart, E. Boyd
San Giovanni Hospital: Dr. Prati, Dr. Imola
LRP Study Endpoints

• For the Test of the Vulnerable Patient Hypothesis
  • The primary endpoint for the test of the vulnerable patient hypothesis will be the increased incidence of NC-MACE within 24 months in patients with increased max 4mm LCBI in all scanned arteries as opposed to those without increased max 4mm LCBI

• For the Test of the Vulnerable Plaque Hypothesis
  • The primary endpoint for the test of the vulnerable plaque hypothesis will be an increased incidence of NC-MACE within 24 months in coronary artery segments with increased max 4mm LCBI as opposed to those without increased max 4mm LCBI
Follow Up Patients
N ~ 1563

Reported Patient-Level Event

Send to Cleveland Clinic Adjudication Team

Send to MCRN Plaque Adjudication Team

Adjudicated Patient-Level Event
Adjudicated Plaque-Level Event

Adjudicated Patient-Level Non-Event
Adjudicated Plaque-Level Non-Event

Cleveland Clinic will identify, if imaging is available, follow up event location

The provided follow up event location guides and drives MCRN Plaque Adjudication Team

Collaborative Effort: Feedback Between Both Teams at Each Step

Reported by the site via EDC
THE LIPID - RICH PLAQUE STUDY

Methodology for Vulnerable Plaque

• Developed a standardized method of determining location of plaques using Ware Segments and Subsegments
• Utilizing systematic, blinded adjudication process guided by Cleveland Clinic

- Ware Segment containing Endpoint Event Culprit Lesion
- Suspected Vulnerable plaque in non-culprit artery scanned at index
- Cause of Index Procedure
- Cause of Follow Up Endpoint Event
The MCRN Plaque Adjudication Team confirms the culprit lesion provided by Cleveland Clinic and translates the culprit vessel into standardized Ware Segments and Subsegments.

**Ware Segments**
- 30 mm each; 120 mm total
- Proximal, Mid, Distal, and Distal Distal

**Ware Subsegments**
- 10 mm; 3 per segment
- Ex: prox 1, prox 2, prox 3
THE LIPID - RICH PLAQUE STUDY

LRP Cumulative Enrollment

- Ending 2 year follow up window April 2018

Enrolled Complete Mar 2016

2yr Follow Up Group
THE LIPID - RICH PLAQUE STUDY

Progress of Follow-up

Follow-up Progress

- 60 Day: 87% completed, 5% missed, 0% death, 8% in window
- 180 Day: 92% completed, 5% missed, 0% death, 3% in window
- 365 Day: 92% completed, 5% missed, 0% death, 3% in window
- 730 Day: 83% completed, 7% missed, 0% death, 8% in window

8% left to complete
THE LIPID - RICH PLAQUE STUDY

LRP Events Distribution

Accumulation of MACE Events

- Cardiac Arrest: 4
- Cardiac Death: 25
- Non Fatal MI: 81
- ACS: 125
- Revascularization: 170
- Progressive Angina: 311
Planned to report Study Results in the fall of 2018
1. Vessels/Lesions with Lipid Rich Plaques cause more MACEs

2. Patients with Non Culprit Lipid Rich Plaques have worse outcome

3. Visible difference but not significant for the prespecified threshold

4. No difference at all
PROSPECT II Study

900 pts with ACS at up to 20 hospitals in Sweden, Denmark and Norway (SCAAR)

NSTEMI or STEMI >12º

IVUS + NIRS (blinded) performed in culprit vessel(s)

Successful PCI of all intended lesions (by angio ± FFR/iFR)

Formally enrolled

3-vessel imaging post PCI

Culprit artery, followed by non-culprit arteries

Angiography (QCA of entire coronary tree)

IVUS + NIRS (blinded) (prox 6-8 cm of each coronary artery)

Clinical FU for 15+ years
Sealing and Shielding of Plaques After Scaffold Implantation

Example of capping a calcified plaque

Brugaletta S et al. Atherosclerosis 2012
PROSPECT II Study

PROSPECT ABSORB RCT

900 pts with ACS after successful PCI

3 vessel IVUS + NIRS (blinded)

≥1 IVUS lesion with ≥65% plaque burden present?

Yes

Absorb BVS + GDMT

Routine angio/3V IVUS-NIRS FU at 2 years

Clinical FU for 15+ years

No

GDMT alone

R 1:1
PROSPECT II Study
PROSPECT ABSORB RCT

900 pts with ACS after successful PCI
3 vessel IVUS + NIRS (blinded)
≥1 IVUS lesion with ≥65% plaque burden present?

routine angio/
3V IVUS - NIRS FU at 2 years

Absorb BVS + GDMT
GDMT alone

1:1

Enrollment closed in Dec 2018 with 901 patients!
Follow-up is ongoing

Clinical FU for 15+ years
Fourier Trial: Effect of Evolocumab on LDL-C

- Placebo (median 92 mg/dL)
- Evolocumab (median 30 mg/dL)

59% mean reduction

Evolocumab: Effect of Timing of Qualifying MI

**Qualifying MI < 2 Years Ago**
- Placebo: 10.8%
- Evolocumab: 7.9%
- HR 0.76
- 24% RRR

**Qualifying MI ≥ 2 Years Ago**
- Placebo: 9.3%
- Evolocumab: 8.3%
- HR 0.87
- 13% RRR

Interaction $P = 0.18$
Fourier Outcome in Patients with and without PAD

**Placebo**
- N=3,642
- HR 0.79
- 95% CI (0.66–0.94)
- P=0.0098

**Evolocumab**
- 3.5% ARR
- NNT 29
- 16.8%
- 13.3%

**No PAD**
- N=23,922
- HR 0.86
- 95% CI (0.80–0.93)
- P<0.001
- 1.6% ARR
- NNT 63

*p-interaction = 0.40*

1. If positive, the trial will promote a widespread use of IVUS-NIRS imaging in non culprit vessels

2. Conventional secondary prevention measures may need to be complemented by focal treatment of lipid rich non culprit lesions (if vulnerable plaque hypothesis wins) or more aggressive systemic treatment of patients with Lipid Rich plaques in non culprit vessels

3. Complemented by non invasive screening of high risk individuals (MSCT) NIRS-IVUS may find application also for finetuning primary prevention in patients with severe lipid rich atherosclerotic burden