Small artery disease (SAD) and medial artery calcification (MAC) are changing the fate of CLI patients
- SAD is a major cause of CLTI

- MAC is strongly associated with PAD

- Are SAD & MAC the same non-atherosclerotic disease?

- SAD-MAC is a leading actor in CLI pts

SAD: small artery disease  
MAC: medial artery calcification
<table>
<thead>
<tr>
<th>Aggregated segments</th>
<th>Risk factors for CLTI</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATG</td>
<td></td>
<td>0.53 (0.26 - 1.1)</td>
</tr>
<tr>
<td>SFA</td>
<td></td>
<td>0.51 (0.29 - 0.89)</td>
</tr>
<tr>
<td>P-TPT</td>
<td></td>
<td>1.17 (0.68 – 2.01)</td>
</tr>
<tr>
<td>Prox BTK</td>
<td>0 artery ref.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 artery 1.7 (0.76 - 3.83)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 arteries 1.86 (0.72 - 4.83)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 arteries 4.84 (1.12 - 20.88)</td>
<td></td>
</tr>
<tr>
<td>Dist BTK</td>
<td>0 artery ref.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 artery 1.69 (0.74 - 3.87)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 arteries 5.81 (1.91 - 17.62)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 arteries 5.71 (1.03 - 31.78)</td>
<td></td>
</tr>
<tr>
<td>BTA vessels</td>
<td>Any of BTA and Arch</td>
<td>13.25 (1.69 - 104.16)</td>
</tr>
</tbody>
</table>
SAD is strongly and independently associated with CLTI, diabetes and dialysis and must be considered as a leading actor in CLTI.
- SAD is a major cause of CLTI

- MAC is strongly associated with PAD

- Are SAD & MAC the same non-atherosclerotic disease?

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SAD: small artery disease
MAC: medial artery calcification
What is MAC?

MAC, also known as Mönckeberg's medial sclerosis, occurs independently of atherosclerosis and is strongly associated with aging, DM and CKD. MAC tends to affect the artery diffusely, appearing as a linear contiguous rail-track pattern of calcification on plain radiography.

**MAC is a strong marker of future cardiovascular events and death**


MAC & PAD are strongly associated

Histopathological studies on amputated limbs of patients with PAD demonstrated that MAC is highly prevalent, suggesting MAC as one of the main determinants of PAD, in combination or not with atherosclerosis.

MAC and elevated ABI are associated with foot ulcer, occlusive PAD and amputation.


N. Narula et al., “Pathology of Peripheral Artery Disease in Patients With Critical Limb Ischemia,” J. Am. Coll. Cardiol., vol. 72, no. 18, pp. 2152–2163, 30 2018


The wrong concept: MAC as a non-obstructive disease

Despite this strong association between MAC and PAD, the interaction in determining the clinical manifestations of the disease is still unknown, essentially because MAC is considered by most authors a “non-obstructive” disease.

Due to this concept, the hypothetic “mechanisms of action” are supposed to be indirect effects of the arterial wall stiffening: loss of vasomotion and adverse remodeling predisposing to an accelerated vascular aging, atherosclerosis and plaque rupture.


P.-W. Fok and P. Lanzer, “Media sclerosis drives and localizes atherosclerosis in peripheral arteries,” PloS One, vol. 13, no. 10, p. e0205599, 2018
SAD-MAC in CLI

- SAD is a major cause of CLTI
- MAC is strongly associated with PAD
- Are SAD & MAC the same non-atherosclerotic disease?
- SAD-MAC is a leading actor in CLI pts

SAD: small artery disease
MAC: medial artery calcification
At the best of our knowledge, SAD and MAC were never considered directly correlated. However, in our daily practice in treating CLTI patients, we very often observe their coexistence, raising the question if they could be expression of different pathophysiological conditions or of the same underlying non-atherosclerotic disease, leading to common clinical symptoms.
In our daily practice we observe a strong association between SAD & MAC.
Study on MAC-score & SAD-score

Pts selection criteria

- 2014-2018
- Consecutive CLTI pts → WIfI Ischemia grade 3
- Tissue loss → RTF 5-6 = WIfI Wound 1-2-3
- **Pts with a detailed angiographic imaging of the foot vessels in 2 projections**
- **Patients living in our region followed in our outpatient clinic**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>221</td>
<td>100%</td>
</tr>
<tr>
<td>Mean age</td>
<td>74 yy</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>194</td>
<td>76%</td>
</tr>
<tr>
<td>DM</td>
<td>191</td>
<td>86%</td>
</tr>
<tr>
<td>ESRD-HD</td>
<td>53</td>
<td>24%</td>
</tr>
<tr>
<td>Limbs</td>
<td>259</td>
<td>100%</td>
</tr>
<tr>
<td>WIfI-WOUND 1</td>
<td>37</td>
<td>14%</td>
</tr>
<tr>
<td>WIfI-WOUND 2</td>
<td>198</td>
<td>77%</td>
</tr>
<tr>
<td>WIfI-WOUND 3</td>
<td>24</td>
<td>9%</td>
</tr>
<tr>
<td>Mean FU</td>
<td>19 months</td>
<td>(3-59)</td>
</tr>
</tbody>
</table>

Preliminary analysis, preparing for publication
<table>
<thead>
<tr>
<th>No SAD</th>
<th>Moderate SAD</th>
<th>Severe SAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of disease or mild disease with a well-represented network of forefoot and calcaneal arteries</td>
<td>Diffuse disease with narrowing and poverty of arch, metatarsal, digital and calcaneal arteries</td>
<td>Occlusion or severe disease with extreme poverty of arch, metatarsal, digital and calcaneal arteries</td>
</tr>
</tbody>
</table>
MAC-score

- 5-steps MAC-score
- Simple foot X-ray: latero-lateral and antero-posterior
- Look for “rail-tracking” calcification length

MAC-score

0-1
≥20 mm

0-1
≥10 mm

0-1
≥10 mm
Distribution in 259 CLTI-limbs

**MAC-score**
- Severe MAC: 44%
- Moderate MAC: 35%
- No MAC: 21%

0-1 = no-MAC
2-3 = moderate MAC
4-5 = severe MAC

**SAD-score**
- Severe SAD: 45%
- Moderate SAD: 29%
- No-SAD: 26%

Preliminary analysis, preparing for publication
## MAC-score versus SAD-score

### Preliminary analysis, preparing for publication

<table>
<thead>
<tr>
<th>MAC-score</th>
<th>sensitivity</th>
<th>specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 no-MAC</td>
<td>100 %</td>
<td>98.1 %</td>
</tr>
<tr>
<td>2-3 moderate MAC</td>
<td>99.1 %</td>
<td>92.7 %</td>
</tr>
<tr>
<td>4-5 severe MAC</td>
<td>100 %</td>
<td>98.1 %</td>
</tr>
</tbody>
</table>
SAD & MAC are the same disease!
From now on I will talk about SAD-MAC
- SAD is a major cause of CLTI
- MAC is strongly associated with PAD
- Are SAD & MAC the same non-atherosclerotic disease?
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SAD: small artery disease
MAC: medial artery calcification
Healing rate

Global population

MAC-score groups

SAD-score groups

Preliminary analysis, preparing for publication
Limb salvage

Global population

MAC-score groups

SAD-score groups

Preliminary analysis, preparing for publication
Survival

Global population

MAC-score groups

SAD-score groups

Preliminary analysis, preparing for publication
Survival

Global population

MAC-score groups

SAD-score groups

Preliminary analysis, preparing for publication
Amputation-free survival

Global population

MAC-score groups

SAD-score groups

Preliminary analysis, preparing for publication
Freedom from foot surgical reintervention

Global population

MAC-score groups

SAD-score groups

The “salami” effect!

Preliminary analysis, preparing for publication
Freedom from redo-PTA

Global population

MAC-score groups

SAD-score groups

The “DRG factory”

Preliminary analysis, preparing for publication
SAD-MAC is a single non-atherosclerotic disease and must be considered the leading actor in CLTI. CLTI pts with high SAD-MAC scores present at 2yy:
- only 30% healing rate without reulceration
- double risk of major amputation and death
- higher rate of foot and vascular reinterventions

These no-option CLTI pts should be considered for alternative therapies such as:
- primary major amputation
- palliative care
- foot vein arterialization

In the last 50 yy our attention was focalized on pure atherosclerotic BAD-PAD, for which we developed wonderful weapons: bypass, PTA, drugs. Now we are facing a worldwide epidemic of old/DM/CKD CLTI pts that are not pure-BAD-PAD.
Small artery disease (SAD) and medial artery calcification (MAC) are changing the fate of CLI patients.