Vascular disease in diabetic patients: what is different?

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Disclosure

Speaker name:
E Ducasse

- I have the following potential conflicts of interest to report:

Consulting

Abbott, Alvimedica, Bard, Biotronik, Boston-scientific, Cook, Cordis, Gore, Lutonix, Medtronic, Spectranetic
1-EPIDEMIOLOGY
World Incidence of Diabetes in 2013

- 382 M people living with diabetes
- 37 M people in North America and Caribbean
- 56 M people in Europe
- 35 M people in Middle East and North Africa
- 72 M people in South-East Asia
- 138 M people in Western Pacific

46% undiagnosed
Diabetes is associated with a high Morbi-Mortality.
Provisional Increase for 2035

- **World**: 592 M people living with diabetes in 2035, an increase of 55% from 2013.
- **2013**: 382 M
- **Increase**:
  - AFR: 109.1%
  - MENA: 96.2%
  - SEA: 70.6%
  - SACA: 59.8%
  - WP: 46%
  - NAC: 37.3%
  - EUR: 22.4%
2-HIGHER MORTALITY

• CLI on diabetic patients = major risk of death

“… diabetes is a state of premature cardiovascular death which is associated with chronic hyperglycaemia …”

Fisher M. et Al, Practical Diabetes Int 2001; 18: 183

“… their prognosis is in many ways similar to that of some malignant forms of cancer.”

TASC 2000, (S171)
PAD/CLI in diabetic patients

• Same physiopathology **BUT:**
  – Higher prevalence
  – Earlier start of the disease
  – Faster evolution
  – More severe clinical manifestations
  – More distal lesions / common multilevel disease
  – Neuropathy → diabetic foot ulcer
  – Higher risk of CLI
  – Less resistance to infection

• WHO: Diabetic foot = one of the highest priorities
3-INFECTION

• Less resistance to infection
• Skin infection and moreover bone infection is certainly under-estimated
  – Negative factor for wound healing and limb salvage during FU
  – Call for systematic investigation and diagnosis
## Society for Vascular Surgery WIfI Index

**Wound grade**
- 0: No rest pain
- 1: Small, shallow ulcer
- 2: Deeper ulcer with exposed bone, joint, or tendon, not involving the tissue heel
- 3: Extensive, deep ulcer involving forefoot/midfoot

**Infection grade**
- 0: No symptoms or signs of infection
- 1: Local infection involving only skin, SQ tissue
- 2: Local infection with erythema >2 cm, or involving structures deeper than skin, SQ (eg, abscess, osteomyelitis)

**Ischemia grade**
- 0: TP >60 mm Hg, ABI >0.8
- 1: TP 40-59 mm Hg, ABI 0.6-0.79
- 2: TP 30-39 mm Hg, ABI 0.4-0.59
- 3: TP <30 mm Hg, ABI <0.39

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**Critical factors gradation in patients with CLI**
- Stratifies the risk of amputation at 1 year
- Could help choosing the suitable treatment

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4-poor runoff

- Poor runoff with small vessel (distal distribution) destruction
  
  » defect in Dhh protein for vessel maturation

Hedgehog-Dependent Regulation of Angiogenesis and Myogenesis Is Impaired in Aged Mice

Marie-Ange Renault, Fanny Robbesyn, Candice Chapouly, Qinyu Yao, Soizic Vandierdonck, Annabel Reynaud, Isabelle Bellloc, Elisabeth Traiffort, Martial Runt, Claude Desgranges, Alain-Pierre Gadeau
5-CALCIFICATIONS
Arterial calcifications

• Medial calcification
  – $\uparrow$ length of diabetes = $\uparrow$ Prevalence
  – Morbi-mortality x 1.5
  – Amputation rate x 5.5

  • Major amputation within 6 - 12 months in the absence of significant hemodynamic improvement
  • 85% could be prevented if treated at early stage
Calcification’s characteristics

- **Amount of calcifications:**
  - 1. absent to low
  - 2. moderate
  - 3. important

- **Axial location:**
  - 1. parietal non concentric
  - 2. parietal concentric
  - 3. central

*Detailed cross-sectional study of 60 superficial femoral artery occlusions: morphological quantitative analysis can lead to a new classification*

Mickaël Ohana, Soraya El Ghannushi, Elie Girsowicz, Anne Lejay, Yannick Georg, Fabien Thaveau, Nabil Chakfe, Catherine Roy

1 Radiology Department, 2 Vascular Surgery Department, Neuvel Hôpital Civil-Strasbourg University Hospital, 1 place de l’Hôpital, 67000 Strasbourg, France
Calcification’s localisation

<table>
<thead>
<tr>
<th></th>
<th>Diabetics</th>
<th>Non Diabetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medial calcification</td>
<td>+++ (x30)</td>
<td>+</td>
</tr>
<tr>
<td>Aorto-Iliac calcifications</td>
<td>1.7%</td>
<td>6.2%</td>
</tr>
<tr>
<td>Femoro-popliteal calcifications</td>
<td>75%</td>
<td>43%</td>
</tr>
<tr>
<td>BTK calcifications</td>
<td>81%</td>
<td>57%</td>
</tr>
<tr>
<td>Lesion’s specificity</td>
<td>Occlusions +++ Length &gt; 10 cm +++</td>
<td>+</td>
</tr>
</tbody>
</table>
6-Pre-operative INVESTIGATION

• Continuous Wave (CW) Doppler +++ / ABI :
  – BUT :
    • Calcifications → falsifies ABI , ↓ doppler penetration
    • obesity
    • ulcers over the site of the artery
  – For :
    • every patient > 40 years old
    • with diabetes > 20 years
    • / 5 years
• TCPO2
  – Less altered by calcifications
• Foot radiography or MRI

• But most of all → per-operative arteriography +++
7-Endovascular TREATMENT

• First-line strategy = early revascularization to obtain direct blood flow to the foot

• TASC II recommendations:
  – For all BTK lesions
  – For SFA lesions in CLI patients where in-line flow to the foot can be re-established and where there is medical comorbidity

  — ENDOVASCULAR IS THE FIRST OPTION
  • Primary / secondary patency rates: Bypass > Endovascular
  • BUT:
    – no difference in limb salvage
    – Primary goal = wound healing more than patency
Endovascular approach

- Antegrade approach +++
  - Ipsilateral femoral artery
  - Controlateral femoral artery if obese or proximal SFA lesions
  - Optimal long sheath placement of 4 French

- Wires
  - 0.035’ for the SFA and popliteal artery
  - 0.018’ and 0.014’ for the BTK
  - Wire escalation strategy (stiffer wire)

- Support catheter
  - Improves pushability
  - Facilitates reshaping / exchange of the wire

KEY POINT:
To still progress on wires with SUPPORT CATHETER
CXI® – 0.018” 90 or 150 Lp straigth or angled tip
Crossing the lesion
proximal part of BTK arteries

• CTO analysis:
  • Proximal part: ostial, bifurcations
  • Distal part: landing zone, collaterals to preserve
  • Run-off
  • Possibility of retrograde access

• Endoluminal +++ / subintimal

• Crossing devices
  – Rotatable tip, High frequency mechanical vibration, radiofrequency energy, mechanical jaws
  – Avenger - Wild Cat, Bard – Crosse, Baylis – Powerwire, BSC – Truepath, Cordis – Frontrunner, Coviden – Viance
If unsuccessful: 10-20%

- Retrograde puncture
  - 21-G micropuncture kit
  - Moderate knee flexion
  - Road mapping or fluoroscopy guidance with calcifications
  - No sheath, just support catheter
  - «SAFARI» and procedure resumed by antegrade approach
  - No hemostasis at the puncture site → just balloon inflation
Dilatation first

• Balloons
  – Low-profile balloons
  – 0.014’ and 0.018’
  – RX and OTW
  – Dedicated diameter 1.25 to 4 mm
  – Dedicated length 10 to 200 mm
8-AND AFTER...SCAFFOLDING?
Stents

- Scaffolding often necessary in diabetics
  - To prevent elastic recoil and constrictive remodeling
  - Stenting of TASC C and D femoropopliteal lesions
- BTK :
  - Still controversial
  - Only as bail out
  - Spot stenting
- SES / BES
- **BUT**: In stent restenosis = 18-40% / 1 year
DRUG ELUTING DEVICES

[Chemical structure of paclitaxel]

paclitaxel
The "DEBELLUM"--lower limb multilevel treatment with drug eluting balloon--randomized trial: 1-year results.

Fanelli F¹, Cannavale A, Corona M, Lucatelli P, Widerk A, Salvatori FM.

Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation (DEBATE-BTK): a randomized trial in diabetic patients with critical limb ischemia.

## DES > PTA / DES > BMS

<table>
<thead>
<tr>
<th>Trial name/Author</th>
<th>ACHILLES</th>
<th>DESTINY</th>
<th>Falkowski</th>
<th>YUKON 1 year FU</th>
<th>YUKON 3 years FU</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Arms's comparison</strong></td>
<td>DES vs. PTA</td>
<td>DES vs. BMS</td>
<td>DES vs. BMS</td>
<td>DES vs. BMS</td>
<td>DES vs. BMS</td>
</tr>
<tr>
<td><strong>Patients, No.</strong></td>
<td>200</td>
<td>140</td>
<td>50</td>
<td>161</td>
<td>161</td>
</tr>
<tr>
<td><strong>Rutherford class</strong></td>
<td>3-5</td>
<td>4-5</td>
<td>3-5</td>
<td>3-5</td>
<td>3-5</td>
</tr>
<tr>
<td><strong>CLI patients (%)</strong></td>
<td>-</td>
<td>-</td>
<td>32</td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td><strong>Lesions length (mm)</strong></td>
<td>27</td>
<td>16-19</td>
<td>17.4-18.2</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td><strong>Primary objective</strong></td>
<td>restenosis rates</td>
<td>restenosis rates</td>
<td>restenosis rates</td>
<td>restenosis rates</td>
<td>Amputation and TLR rates</td>
</tr>
<tr>
<td><strong>Follow-up (months)</strong></td>
<td>12</td>
<td>12</td>
<td>6</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td><strong>Patency rate (%)</strong></td>
<td>75 vs. 57 (p=0.025)</td>
<td>85 vs. 54 (p=0.0001)</td>
<td>96 vs. 76 (NS)</td>
<td>80.6 vs. 55.6 (p=0.004)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Restenosis rates (%)</strong></td>
<td>22.4 vs. 41.9 (p=0.019)</td>
<td>21 vs. 47 (p&lt;0.0001)</td>
<td>16 vs. 76 (p&lt;0.001)</td>
<td>19.4 vs. 44.4</td>
<td>-</td>
</tr>
<tr>
<td><strong>Freedom from TLR (%)</strong></td>
<td>90 vs. 83.5 (NS)</td>
<td>91 vs. 66 (p=0.001)</td>
<td>88 vs. 44 (p&lt;0.05)</td>
<td>92.3 vs. 82.5 (NS)</td>
<td>90.8 vs. 80 (p=0.06)</td>
</tr>
<tr>
<td><strong>Major amputation rates (%)</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1.6 vs. 3.2 (NS)</td>
<td>2.6 vs. 12.2 (p=0.03)</td>
</tr>
</tbody>
</table>
DES > DEB

• DES > DEB in long infrapopliteal lesions
  – significantly lower residual immediate post-procedure stenosis
    » 9.6 % vs. 24.8 % ; p < 0.0001
  – significantly reduced vessel restenosis at 6 months
    » 7 of 25 [28%] vs. 11 of 19 [57.9%] ; p = 0.0457

PES BTK-70 study on Stentys presented by Deloose-MEET 2014

• What about BTK Self expanding DES?
  – No superior results at 12 months :
  – Freedom from TLR at 12 Months 76,4%
  – Primary patency rate 69,5%
DEDICATED DES for BTK treatment

• Cre8™ BTK from Alvimedica
• Abluminal reservoir

Abluminal Reservoir Technology

Amphilimus™ Formulation: Sirolimus + organic acid

• Amphilimus™ Formulation: Sirolimus + organic acid
The Amphimilimus™ formulation

**Sirolimus**
- Immunosuppressant
- Anti-proliferative action
- Anti-microbial
- Inhibitor of inflammatory cell activities
- High potency

**Organic acid**
- Sustained drug elution timing
- Modulated drug bioavailability
- Raised homogeneous drug distribution
- Enhanced drug stability

**Proprietary technology**

**Sirolimus and Organic Acid are eluted together**

**Combined effect!!!**
Amphilimus Formulation
= Sirolimus + Fatty Acid

1) Fatty acids are used to improve trans-dermal and skin delivery of many different drugs.*

2) Cardiac fatty acid uptake is double in diabetic mice model.**

* Drug Delivery, 15:373-379, 2008

** Cardiac fatty acid uptake and metabolism in db/+ and db/db mice. Curr Cardiol Rev. 2008 February; 4(1): 12-21
Clinical proofs

- For coronaries
- For BTK

**Cre8 vs. Xience family: a propensity matched analysis**

From San Raffaele Scientific institute & Sant’Ambrogio Scientific institute

150 Cre8 vs. 150 Xience
Take Home Message

- High incidence and prevalence of diabetes with even higher provisional increase
- Associated with high morbi-mortality
  - Severe clinical manifestations / Limb loss
  - Medial calcifications+++ / CLI
- New classifications : WIfI
- Early revascularisation
  → per-operative arteriography
  → endovascular +++
  - crossing and re-entry
  - scaffolding
  - DES > PTA / BMS / DEB and dedicated material
CONCLUSION

• Specific knowledge and adapted treatment is required for CLI management on diabetic
Vascular disease in diabetic patients: what is different?

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