Venous valves-the next frontier

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Senior Consultant Vascular Surgeon
Oslo University Hospital
The aim of deep vein surgery and vein valve reconstruction
Deep venous reflux

Ambulatory venous hypertension
The magnitude of the problem

Venous leg ulcer

• Incidence 15-30 per 100 000/år
• Prevalence 0,4 % -2,4 %

• The total direct annual cost of treatment
  2% health budget in western countries
Deep venous thrombosis → PTS CVI

- PTS 20-50%
  - Venous claudication 15%
  - Leg ulcer 2.8-15%

DVT 50-80/100 000

Quality of life in PTS

- Poorer than arthritis, diabetes, chronic lung disease
- Equal to angina, cancer, congestive heart failure

Kahn SR, et al
**Investigations**

- Color duplex ultrasound
- Ambulatory venous pressure measurement
- Trans-femoral venography
- MR venography

- Quantify and classify reflux
- Assess valve and muscle pump function
- Assess significance of obstruction
- Morphology of post-thrombotic veins
C4, C5-C6 patients

Compression therapy 6 months
Superficial/perforator surgery

Primary CVI

- Reflux
  - Extern valve plasty
  - Intern valve plasty
  - Transposition

Secondary CVI

- Reflux/Obstruction
  - Recanalisation and stenting

Valve Reconstruction

- Auto transplantation
- Neo-valve construction

NOVI
Norwegian National Unit for Reconstructive Deep Venous Surgery
Challenges abolishing post-thrombotic axial reflux

Replacement
Anatomy
Histology
Hemodynamics
Recipient

Endophlebectomy + Valve reconstruction + out flow
# Lessons learned

## Site and number

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Hemodynamic Improvement P 0.014</th>
<th>Durability months P ns</th>
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<tbody>
<tr>
<td>*Only Popliteal reconstruction</td>
<td>14</td>
<td>3</td>
<td>24 (6-108)</td>
</tr>
<tr>
<td>*Popliteal plus</td>
<td>10</td>
<td>7</td>
<td>24 (6-108)</td>
</tr>
<tr>
<td>Non-popliteal</td>
<td>8</td>
<td>0</td>
<td>6 (6-84)</td>
</tr>
</tbody>
</table>

*Rosales A, Venous valve reconstruction. Eur J Vasc Endovasc Surg 2008*
Results after VR
655 patients, 10 materials

• Ulcer healing rate 60%-70%

• Clinical improvement 70%-80%

• Ulcer-free period C5-C6 36 mo. (6-108)

• Durability (3 / 5 years) 47% / 44%

Maleti et al Eur J Vasc Endovasc Surg (2011) 41, 837e848
Durability

What if I am 50 years old?

Fig. 4. Cumulative durability rate of different reconstructions.

Venous valves-the next frontier
Future Perspective

Percutaneous delivered venous valves

Percutaneous valve construction

Tissue Engineering
"tissue engineering a practice of combining scaffolds, cells, and biologically active molecules into functional tissues"
Tissue-engineered allogeneic vein valves in the treatment of chronic venous insufficiency

Mia H. Rambøl a,b,*, Jonny Hisdal b, Jon O. Sundhagen b, Jan E. Brinchmann a,c, Antonio Rosales b

a Norwegian center for stem cell research, Department of Immunology, Oslo university hospital, Oslo, Norway
b Oslo vascular center, Department of Vascular surgery, Oslo university hospital, Oslo, Norway
c Department of molecular medicine, University of Oslo, Oslo, Norway
Research group
Vascular Research

• To establish a multidisciplinary group within TEVG
• Responsability according to field of expertise
• Milestones
TE vascular grafts

- **Natural scaffold: allogeneic and xenogeneic ECM with chemical cues**
- Synthetic biodegradable scaffold
- Gel-based scaffold
- Self-assembled cell-sheet-based techniques
Allo- og xenogeneic donor
Decellularising to isolate the extracellular matrix (ECM) by removing the populating cells of an organ
1. Removal of red blood cells
2. Removal of endothelial and smooth muscle cells
3. Removal of DNA
4. Cold storage of scaffold after sterilization
Source for scaffold

- Human cadaver
- Human long saphenous vein
- Sheep jugular vein
TEVG on-going PhD project

- Implementing the methods of characterization for the decell tissue
  - DNA, collagen, elastin and staining (DAPI)
- The selection of a suitable protocol for decellularization
- The value of proteomic evaluation of decell tissue
TE ongoing PhD project

Proteomic evaluation of decellularized vein tissue for generating ECM scaffold for tissue engineering

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<tr>
<th></th>
<th>Native</th>
<th>Decell</th>
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<tbody>
<tr>
<td>Long saphenous vein</td>
<td>proteomics</td>
<td>proteomics</td>
</tr>
<tr>
<td>Sheep jugular vein</td>
<td>proteomics</td>
<td>proteomics</td>
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# ClexBio’s proprietary technologies

<table>
<thead>
<tr>
<th><strong>CLEX™</strong></th>
<th><strong>VivoSet™</strong></th>
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<tbody>
<tr>
<td><strong>Granted patent (priority March 2015)</strong></td>
<td><strong>Patent pending (priority April 2022)</strong></td>
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<tr>
<td>Competitive Ligand Exchange X-linking (CLEX) is our patent-protected method to create biologically compatible hydrogels. The technology enables the creation of cell-laden microstructures with the use of microfluidics.</td>
<td>VivoSet is a technology that utilizes healthy human cells to grow tissues composed of extracellular matrix. The uniqueness of VivoSet is the ability to grow large tissues rapidly in any chosen geometry, e.g. veins and other conduits.</td>
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![CLEX™ Diagram](image1.png)

![VivoSet™ Diagram](image2.png)

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*After only 1 week incubation!*
CSEM - the best partner for automated tissue engineering
Manufacturing of transplant-ready acellular vein grafts

1. Formulation development & Tissue molding
2. Automated manufacturing
3. Transplant-ready human vein graft

Manufacturing partner: :: csem

Clinical Partner: NOVI, Oslo University Hospital
## Vein graft to CVI market

<table>
<thead>
<tr>
<th>Year</th>
<th>Activities</th>
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<tr>
<td>2022</td>
<td>Automated manufacturing</td>
</tr>
<tr>
<td>2023</td>
<td>In vitro tissue tolerance</td>
</tr>
<tr>
<td>2024</td>
<td>In vivo tissue tolerance</td>
</tr>
<tr>
<td>2025</td>
<td>GMP facility</td>
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<tr>
<td>2026</td>
<td>First-in-man pilot study</td>
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### Regulatory roadmap
- FDA
- Clinical Quality & regulatory manufacturing
- Team expansion

### Clinical Trial
- Phase I (BLS)
Research questions

• Redesigning the scaffold
  – In vitro with stem cells
  – In vivo in the animal modell first