Apheresis Therapy Systems

DALI® & MONET®
Complementary therapies for tailored Lipoprotein Apheresis
Lipoprotein Apheresis for elevated LDL cholesterol and lipoprotein(a) levels:

Lipoprotein Apheresis is a treatment of choice for those homozygous, severe hypercholesterolaemic and hyper-Lp(a) patients, when diet and treatment with lowering agents are not sufficient to achieve desired lowering of LDL-c and Lp(a).

Treatment targets and guidelines according to EAS/ESC guidelines

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Recommended target levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high cardiovascular risk</td>
<td>LDL-c &lt;70 mg/dL (1.8 mmol/L) Lp(a) &lt;50 mg/dL</td>
</tr>
<tr>
<td></td>
<td>• Documented cardiovascular disease</td>
</tr>
<tr>
<td></td>
<td>• Diabetes mellitus (DM) with target organ damage or with a major risk factor such as smoking, hypertension or dyslipidaemia</td>
</tr>
<tr>
<td></td>
<td>• Severe CKD (GFR &lt; 30 mL/min/1.73 m²)</td>
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<tr>
<td></td>
<td>• SCORE ≥10% for 10-year risk of fatal CVD</td>
</tr>
<tr>
<td>High cardiovascular risk</td>
<td>LDL-c &lt;100 mg/dL (&lt;2.6 mmol/L)</td>
</tr>
<tr>
<td></td>
<td>• Markedly elevated single risk factors, in particular cholesterol &gt;310 mg/dL (8 mmol/L) or BP &gt;180/110 mmHg</td>
</tr>
<tr>
<td></td>
<td>• Most other people with DM</td>
</tr>
<tr>
<td></td>
<td>• Moderate CKD (GFR &lt;30–59 mL/min/1.73 m²)</td>
</tr>
<tr>
<td></td>
<td>• SCORE ≥5% and &lt;10% for 10-year risk of fatal CVD</td>
</tr>
<tr>
<td>Moderate cardiovascular risk</td>
<td>LDL-c &lt;115 mg/dL (&lt;3.0 mmol/L)</td>
</tr>
<tr>
<td></td>
<td>• SCORE ≥1% and &lt;5% for 10-year risk of fatal CVD</td>
</tr>
<tr>
<td>Low cardiovascular risk</td>
<td>LDL-c &lt;115 mg/dL (&lt;3.0 mmol/L)</td>
</tr>
<tr>
<td></td>
<td>• SCORE &lt;1% for 10-year risk of fatal CVD</td>
</tr>
</tbody>
</table>

LDL/Lp(a) target levels according to EAS/ESC guidelines

If this cannot be reached the aim is "the lower the better".1,2

Aim of Lipoprotein Apheresis or of lipoprotein-lowering therapy:

Reduction of atherogenic LDL-c and Lp(a) to prevent progression of the atherosclerotic changes or to achieve regression of the pathological processes.

FH patients remain largely underdiagnosed or undertreated and are consequently at high risk.4
**DALI® apheresis – direct removal of lipoproteins from whole blood**

**Lipoprotein Apheresis with DALI®
Direct Adsorption of Lipoproteins**

Features of the DALI® column:
- Selectively binds LDL-c and Lp(a) from whole blood
- Different adsorber configurations for individualised therapy needs:
  - DALI® 500
  - DALI® 750
  - DALI® 1000
  - DALI® 1250
- A sharp reduction in LDL-c (70%) and Lp(a) (65%) following a single treatment session
- Only slightly reducing HDL (15%)

**Treatment with DALI®:
- Venous or AV fistula access can be used
- Anticoagulation:
  - Citrate solution (ACD-A) is used during the priming and continuously throughout the treatment procedure
  - Heparin is used for the priming procedure and is recommended as an initial patient bolus before the treatment
  - ACD-A solution is furthermore used, because it has a reducing effect on the platelet and complement activation induced by the extracorporeal treatment
- The binding of LDL-c and Lp(a) is characterised by electrostatic interaction between the negatively charged polycrylic acid of the adsorber material and the positively charged apolipoprotein B-100 (ApoB-100) of LDL-c, VLDL and Lp(a)

**DALI® – a simple extracorporeal circuit**
Frequency and duration of the treatment:

- Frequency of the treatment ranges between once a fortnight up to twice a week, depending on the national treatment guidelines and the clinical condition of the patient.
- The system configuration selected and the blood volume to be treated depend on the patient's clinical condition.
- The recommended treatment volume is 1.6 x the patient's blood volume.
- Depending on the patient's clinical situation, a blood flow rate of 80 mL/min is commonly used.
- Depending on the blood volume to be treated and the treatment speed, the apheresis session lasts one to two hours.

Benefits of DALI® treatment:

- Highly selective for LDL-c and Lp(a) removal.
- Significantly effective in LDL-c and Lp(a) reduction.
- Short treatment time (1–2 h).
- Simple treatment procedure.

Contraindications:

ACE inhibitors (e.g. Enalapril, Ramipril, Lisinopril, etc.), as well as combination drugs which contain ACE inhibitors (e.g. Sincronium, Triveram, Cibadrex, Capoten), are contraindicated due to the bradykinin release caused by the contact activation of the prekallikrein system induced by the negatively charged adsorber surface. This can also apply for other drugs, which influence the bradykinin regulation (synthesis or inhibition of metabolism).

AT₁ inhibitors are not contraindicated for the use of DALI®.
Therapeutic apheresis with MONET®
Membrane Filtration Optimised Novel Extracorporeal Treatment

Features of MONET®:

• Utilises Fresenius Medical Care’s core competence in fibre and membrane manufacturing
• The plasma fractionator MONET® is made of a Fresenius Polysulfone® membrane with a surface area of 2.0 m²
• MONET® is a two-step procedure
  - First step: plasma separation by centrifugation or filtration
  - Second step: the separated plasma is passed through the MONET® plasma fractionator
  If TMP increases, rinsing of the MONET® plasma fractionator with saline can be performed

Treatment with MONET®:

• Venovenous or AV fistula access can be used
• High molecular and rheological-relevant components are retained
• Customised anticoagulation can be carried out depending on the patient needs

Four different anticoagulation regimes are possible:

• ACD-A continuously throughout the treatment procedure
• Heparin continuously throughout the treatment procedure
• ACD-A and Heparin combined continuously throughout the treatment procedure
• Heparin manually during the treatment procedure or just as an initial patient bolus before the treatment
**MONET® – effective reduction of macromolecules**

<table>
<thead>
<tr>
<th>Mean reduction rates of MONET®</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lp(a)</td>
<td>~70%</td>
</tr>
<tr>
<td>LDL-c</td>
<td>~64%</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>~58%</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>~50%</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>~51%</td>
</tr>
<tr>
<td>HDL-c</td>
<td>~23%</td>
</tr>
<tr>
<td>IgM</td>
<td>~40%</td>
</tr>
<tr>
<td>IgA</td>
<td>~23%</td>
</tr>
</tbody>
</table>

**Benefits of MONET® treatment**

- Effective reduction of LDL-c and Lp(a)
- Rheological benefits through the reduction of macromolecules fibrinogen and immunoglobulins
- Broad range of indications possible
- Substantiated filtration procedure

**Contraindications**

There are no listed contraindications for the use of MONET® plasmafractionator.

**The setup of DALI® & MONET®**

- Both systems, DALI® and MONET®, can be carried out with the haemoadsorption machine Art Universal
- Additionally, MONET® can be carried out with a blood cell separator/centrifuge (e.g. COM.TEC®)
Safety of DALI® & MONET®

Clinical studies show low side effects

The general safety of Lipoprotein Apheresis has been demonstrated in a number of studies. The reported side effect rate is below 4%\(^9\). Studies have shown that the side effect rate of DALI® and MONET® ranges between 0.5%\(^9\) and 3.85%\(^1\).\(^2\)

The key results of the multicentre observational study LINET (Non-interventional study evaluating efficacy and safety of DALI® and MONET® systems in routine clinical practice) are listed below.\(^9\)

The LINET study:
- Prospectively evaluated 2,154 DALI® and 1,297 MONET® sessions
- 122 patients enrolled
- Observation period over two years
- Safety parameters included clinical side effects (adverse device effects), changes in laboratory parameters and technical complications

Results of the LINET study:
- Clinical and technical complications were low, with a frequency of 0.5% per treatment
- The majority of events were not serious with transient hypotension and puncture problems being the most frequent ones
- Changes of blood count and proteins were typically transient but regular laboratory investigations are recommended for long-term application

Documented adverse device effects\(^9\)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of events MONET®</th>
<th>DALI®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paleness</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Vomitus</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Oedema</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>18</td>
</tr>
</tbody>
</table>

No. of treatments with event(s), % 0.4 0.5

DALI® & MONET® – proven clinical effectiveness

Long-term study results underscore the selectivity of the DALI® system for lipid lowering in high double-digit levels\(^5\)

Reduction rates with MONET® therapy show strong results for Lp(a) and LDL-c as well as being effective for fibrinogen with a reduction of >50\%\(^5,\,6,\,10,\,11\)

Comparison of DALI® and MONET® performances\(^5,\,7,\,11\)
Effect of the DALI® treatment on the clinical outcome shown by an observational retrospective study

In a retrospective observational study, patient files and questionnaires of 18 chronic patients treated with DALI® were evaluated to determine the rate of CV events and clinical outcomes respectively.

Result of the study:
Reduction of the mean annual event rate per patient

0.48 before and 0.09 (P <0.004) after the start of DALI® therapy

Long-term observation of coronary events after the start of DALI® therapy

Risk reduction in coronary incidents by Lp(a) reduction underline the value and relevance of Lipoprotein Apheresis

The prospective observational multicentre study of Leebmann et al. demonstrated in patients with elevated Lp(a) and progressive cardiovascular disease under maximally tolerated lipid lowering medication, that Lipoprotein Apheresis effectively lowered the incidence rate of cardiovascular events. Two years before and two years after the start of apheresis therapy were compared.

Effectively lowered incidence rate of cardiovascular events by apheresis

Adapted from Leebmann et al.; Circulation 2013;128:2567-2576

Cardiovascular risk reduction by Lipoprotein Apheresis

Adapted from Bosch & Keller; Therapeutic Apheresis & Dialysis 2003;7(3):341-344
With DALI® and MONET® we offer you complementary therapies for the tailored treatment of your hyperlipidaemic patients, delivered through one machine

**DALI®**
- Easy-to-use whole blood adsorber
- Fast treatment, duration only 1–2 h
- Different configurations for individualised therapy needs
- High selectivity to eliminate LDL-c and Lp(a)

Typical patient profile for DALI® treatment:
- Elevated LDL-c and/or Lp(a) level
- Using AT₁ antagonists in place of ACE inhibitors or other bradykinin affecting drugs

**MONET®**
- Substantiated filtration procedure
- Rheological and Lipoprotein Apheresis
- Removal of large molecules (Lp(a), LDL-c, fibrinogen, IgM, IgA)
- Many indications possible

Typical patient profile for MONET® treatment:
- Elevated LDL-c and/or Lp(a) level
- Being on ACE inhibitors or other bradykinin affecting drugs
- Need for additional fibrinogen lowering

DALI® apheresis – direct removal of lipoproteins from whole blood

MONET® – effective reduction of macromolecules
DALI® & MONET® – treatment kits contain all necessary equipment
References

(3) Adapted from Heart UK Toolkit, document 3.1., February 2012.
(6) Rambow et al.; Efficacy of lipid reduction with DALI® and MONET® apheresis techniques – results from a multicenter observational study; 4th Dresden International Symposium on Therapeutic Apheresis, 2016.
(11) Ringel; Atherosclerosis Supplements 2010;11(2):126.

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