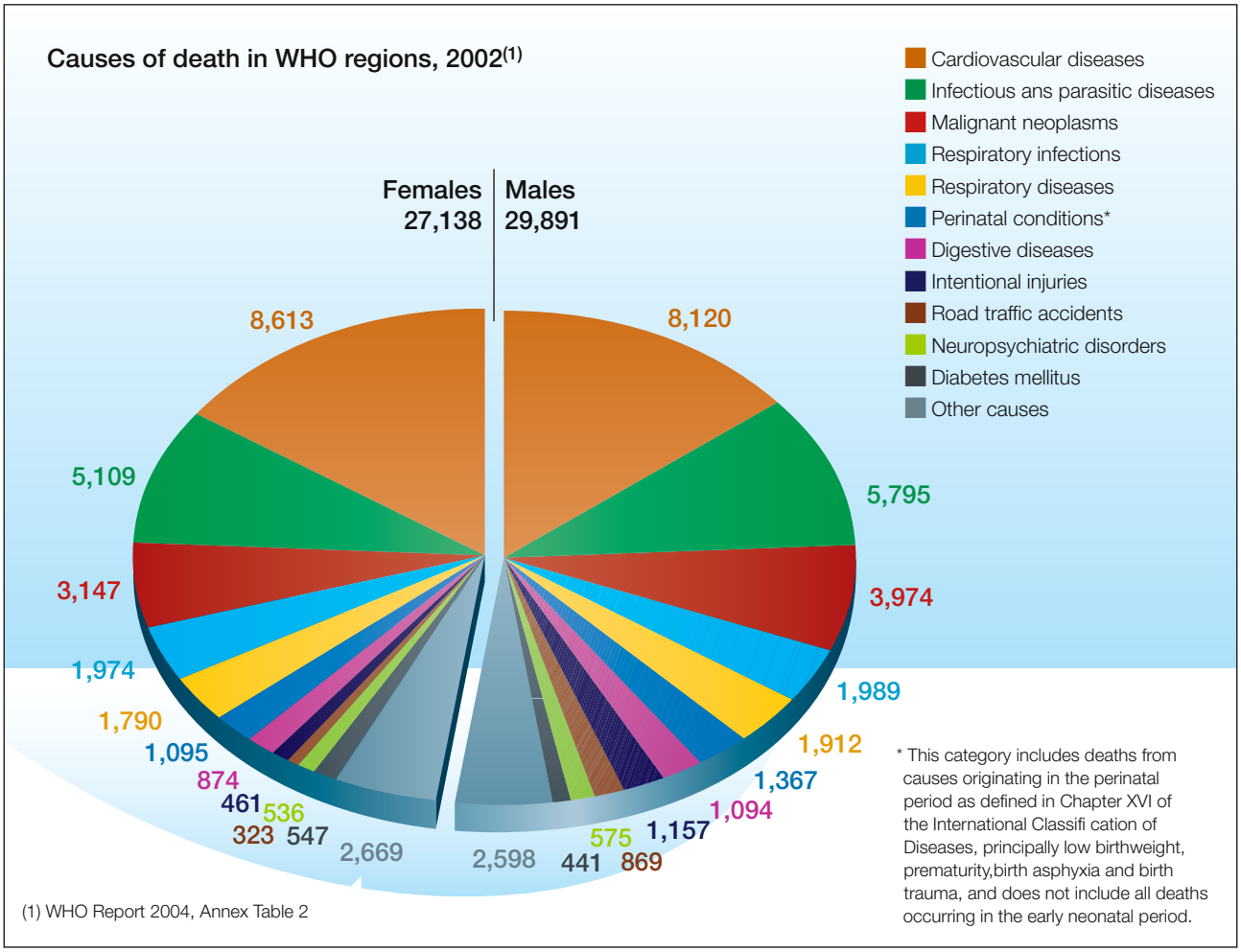
Therapeutic Apheresis

DALI®

Direct Adsorption of Lipoproteins

Fresenius Medical Care

Hypercholesterolaemia – Risk factor LDL cholesterol



A raised LDL cholesterol level is one of the most important risk factors in the development of arteriosclerosis and thus coronary heart disease (CHD). Cardiovascular disease is the No. 1 cause of death; with coronary heart disease accounting for the largest share.

In 2002 there were 57 million deaths worldwide, with 29 dying of the consequences of cardiovascular disease.

Despite the development of newer efficacious drugs there are some patients whose elevated LDL-cholesterol could not be treated sufficiently.

A challenge to science:

- 10 million people throughout the world suffer from familial hypercholesterolaemia
- For example, 160,000 patients are affected in the Federal Republic of Germany
- CHD manifests itself in 60–71% of men between the age of 40 and 50
- 50% of men who do not receive treatment will die of an acute heart attack before reaching 60
- in about 6,000 patients in Germany diet and medication are not enough*

* W. März, J. Kreuzer. Der Lipidreport 2 (2002) 3

Patients with familial hypercholesterolaemia – when diet and medication are not enough

The disease of familial hypercholesterolaemia (FHC) distinguishes between two genetically determined forms: the homozygous (frequency 1:1,000,000) and the heterozygous (1:500) patients.

For homozygous patients it is not possible to bring about an effective reduction in LDL cholesterol through diet or pharmacological means. Early LDL apheresis, performed regularly, is currently the only option for reducing LDL cholesterol in these patients, and also improving their prognosis in terms of primary prevention.

The treatment of heterozygous high-risk patients with marked hypercholesterolaemia remains a problem in terms of secondary prevention.

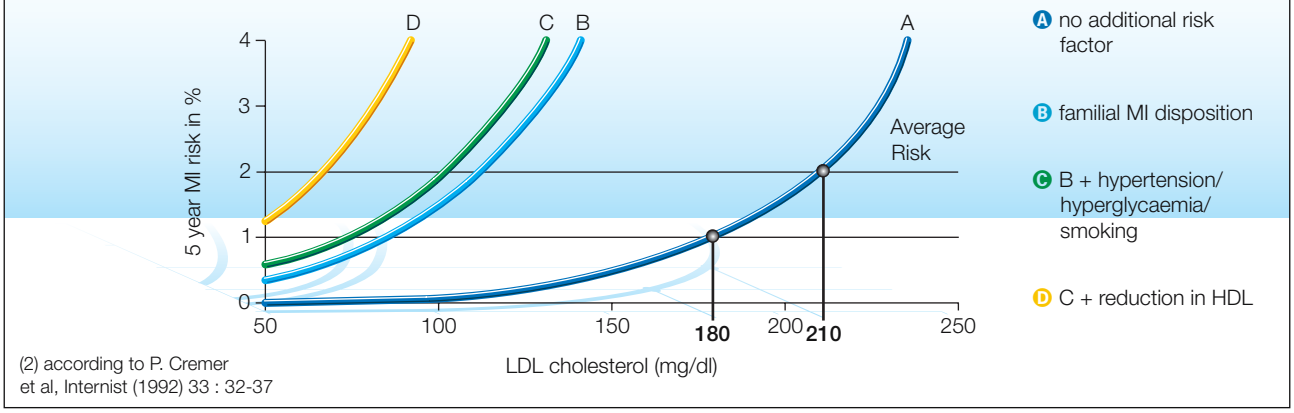
These patients show additional risk factors, e.g. hypertension. The risk of these patients suffering another cardiovascular incident increases by a factor of ten. The probability of a recurrent infarction is considerably greater still.

Even with maximum combination therapy involving diet and medication, it is not possible to provide adequate treatment (< 70 mg/dL)* for these patients. In such cases, LDL apheresis is also indicated.

In addition, the atherogenic effect of a raised Lp(a) level has come under discussion. For patients with a raised Lp(a), LDL apheresis is the sole effective therapy option available in terms of secondary prevention.

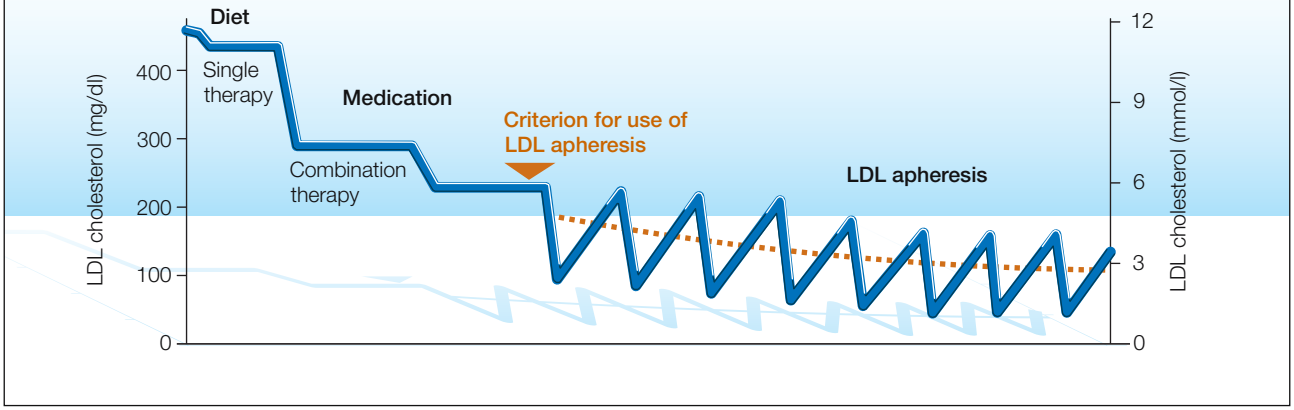
* Grundy et al, Circulation 110 (2004) 227

Myocardial infarction-risk as a function of LDL cholesterol and additional risk factors(2)



(2) according to P. Cremer et al, Internist (1992) 33 : 32-37

Therapy stages with hypercholesterolaemia



LDL apheresis with DALI®

The central element of DALI® LDL apheresis is the adsorber column. The carrier material selectively binds LDL cholesterol and Lp(a) from whole blood.

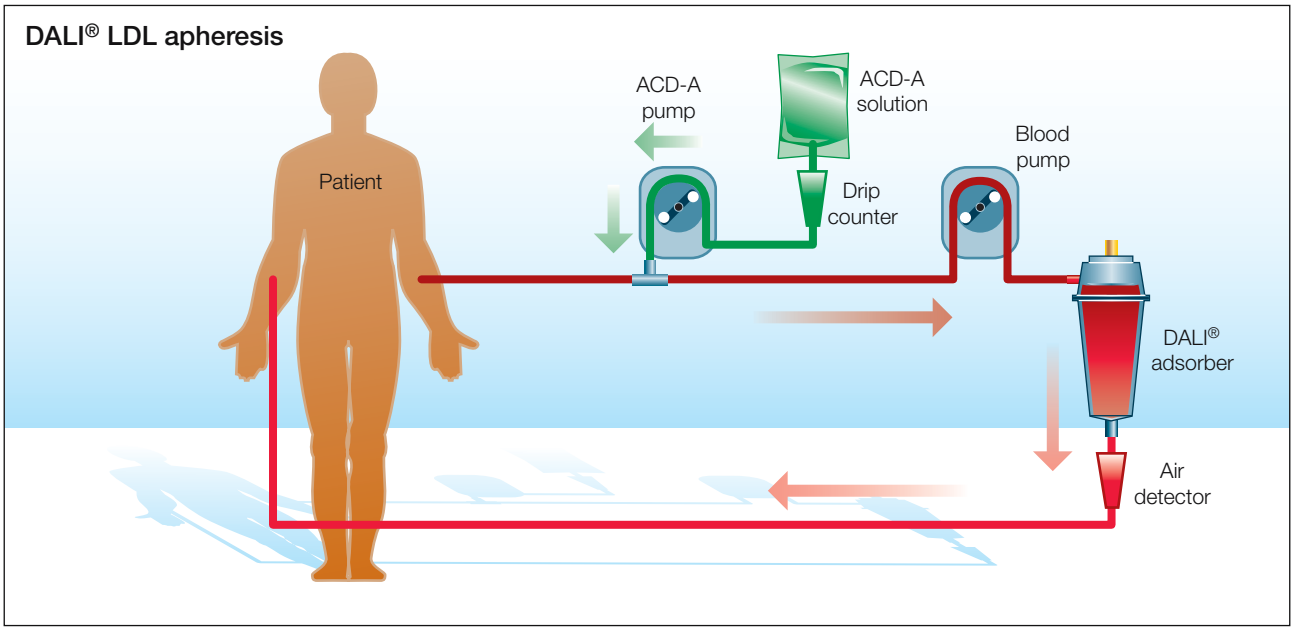
The aim of the treatment is to reduce the atherogenic LDL cholesterol or Lp(a) to prevent progression of the atherosclerotic changes or achieve regression of the pathological processes.

Reduction of the LDL cholesterol can be individually adapted to each patient by means of different adsorber sizes. During a treatment, LDL cholesterol can be reduced by between 64% and 76%.

DALI® LDL apheresis

During extracorporeal therapy a venovenous procedure is generally used. The blood is drawn from a vein in the patient's arm, passed through the adsorber and then returned via the other brachial vein. Citrate solution (ACD-A) is used as an anticoagulant throughout the procedure. In the adsorber the LDL cholesterol or Lp(a) is bound selectively and removed from the whole blood.

In order to tailor the treatment to individual patients, a range of adsorbers is available (DALI® 500, DALI® 750) which can be combined with each other. Monitoring of the extracorporeal circulation is carried out with the 4008 ADS/*Art* haemoadsorption unit.



Duration of treatment

The frequency of treatment ranges between once a fortnight and twice a week. Depending on the blood volume to be treated and the therapy speed, the apheresis session lasts one to two hours.

Features and benefits of treatment

- Acute reduction in LDL cholesterol by up to 76%
- With patients undergoing maximum drug therapy the mean LDL level is reduced by a further 40–50% in the long term
- Increase in HDL cholesterol
- Improvement in LDL/HDL ratio
- Improvement in rheological properties of blood (e.g. reduction in erythrocyte aggregation)
- Halt in progression or even regression of atherosclerosis
- Over 150,000 treatments performed on more than 650 patients worldwide

Safety and effectiveness

The safety of DALI® whole blood treatments has been demonstrated in a number of studies. The key results are listed below:

The performance and safety of the DALI® system (DALI® 500, DALI® 750 and DALI® 1000) was investigated during an initial multicentre study[3] performed on 14 patients. During 238 treatments there was only a total of 8 undesirable events (3.4%) which were directly associated with DALI® therapy. The side effects described were not marked and were all easily controlled.

Apart from LDL and Lp(a) all other blood parameters were barely affected (e.g.: HDL, albumin, electrolytes) due to the system-specific selectivity. Another multicentre long-term study[4] performed on 63 patients at 30 centres over 2 years showed that the treatment was well tolerated. In this study a total of 2156 treatments were performed.

In the initial multicentre study[3] mentioned above, three different system configurations were investigated to achieve an optimum acute and long-term LDL reduction for patients with different blood volumes and different cholesterol values. The range of adsorber sizes (DALI® 500, DALI® 750, DALI® 1000) allows treatment to be tailored to each patient.

In the case of patients with additionally raised atherogenic Lp(a) this risk factor can also be reduced by between 59% and 70% thanks to the effectiveness and selectivity of the process.

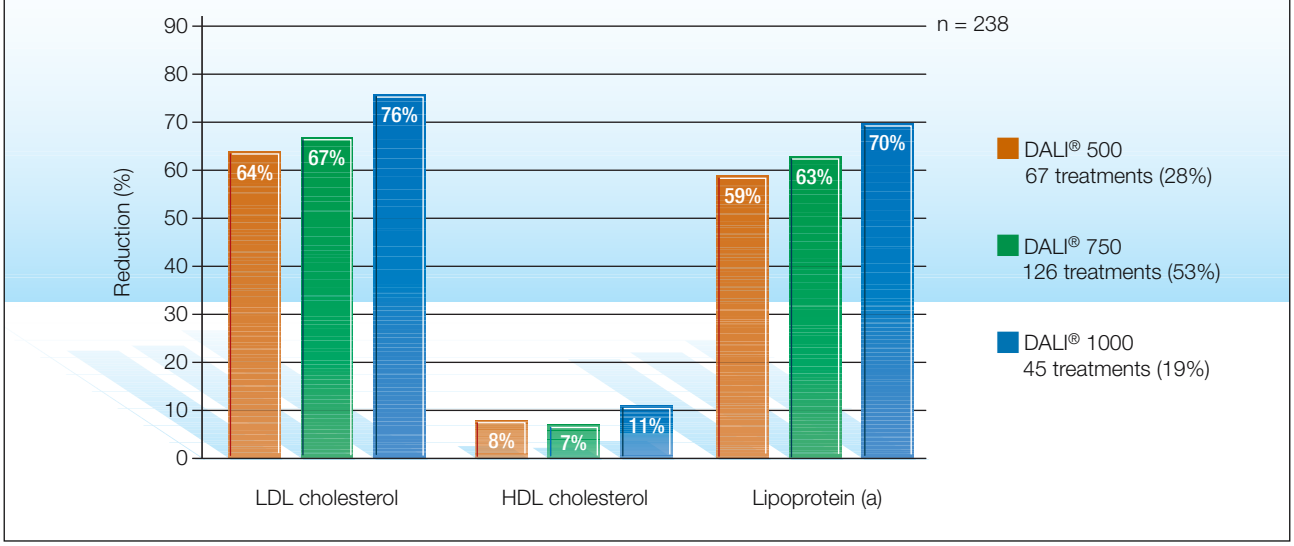
In contrast to other processes there was virtually no change in atheroprotective HDL levels.

(3) Dräger et al, Eur J Clin Invest 28 (1998) 994-1002
(4) Bosch et al, J Clin Apheresis 17 (2002) 161-169

Side effect		Treatments*
Cardiovascular	e.g.: vertigo, hypotension	50 (2.3%)
Hypocalcaemia	e.g.: paraesthesia	27 (1.3%)
Poor tolerance	e.g.: heat sensation, flushing	21 (0.9%)
Total		98 (4.5%)

* In some patients several side effects occurred simultaneously or in different treatments.

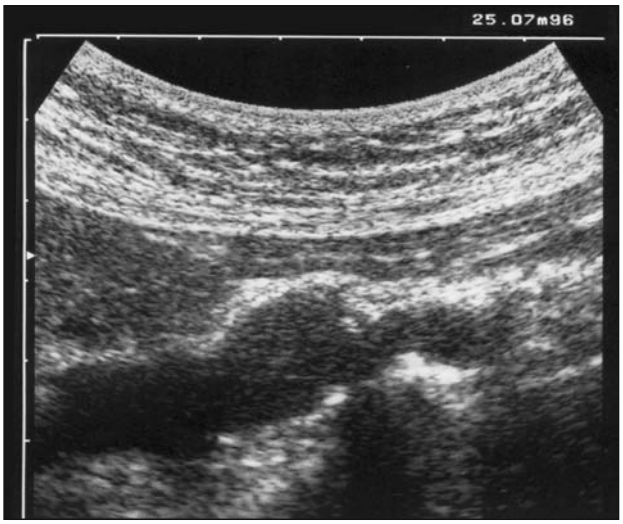
Reduction rate with DALI® adsorber[3]



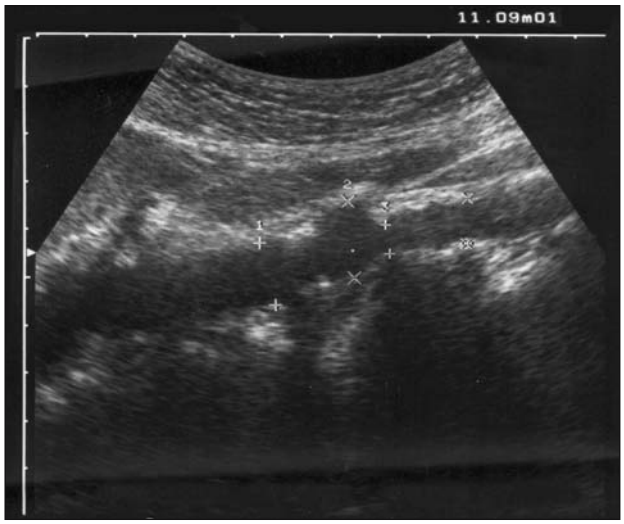
The following results were achieved in the above long-term study[4]: there was an acute reduction in LDL cholesterol by 69%, and Lp(a) by 64%. The long-term reduction in LDL when comparing the preapheresis value before inclusion in the study with the interapheresis value of the last treatments, was 42% for all patients, and 46% for patients who had not previously undergone apheresis treatment.

It should be emphasised that with LDL apheresis using DALI®, atheroprotective HDL can be increased in the long term in addition to the effect of drug therapy.

Example of successful DALI® therapy



Patient with severe familial, heterozygous hypercholesterolaemia and poor tolerance of CSE inhibitors.



No progression of atherosclerotic lesion over 5 years.

Fresenius Medical Care

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