Prospective randomised cross-over comparison of three LDL-apheresis systems in statin pretreated patients with familial hypercholesterolaemia

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Abstract

Various LDL-apheresis systems have gained wider clinical acceptance in recent years to treat patients with severe familial hypercholesterolaemia, in particular in patients with coronary artery disease. For each single device data on efficacy have been provided, but up to now no comparative analysis including the novel direct adsorption of lipoproteins from whole blood has been reported. This prospectively designed cross-over comparison of three commercially available LDL-apheresis systems (immunoadsorption, IMAL; dextran sulphate adsorption, DSA; direct adsorption of lipoproteins, DALI) was performed in eight patients with homozygous (n = 3) and heterozygous (n = 5) familial hypercholesterolaemia. Removal of atherogenic lipoproteins was highly effective in all systems, for LDL-cholesterol in particular: DSA: 84.3 ± 6.2%; IMAL: 82.1 ± 8.3%; DALI: 76.6 ± 7.2% (P < 0.05 as compared DALI versus IMAL and DSA). A reduction in Lp(a) of about 63% was achieved by each device. Loss in HDL-cholesterol was highest with IMAL (-21.3 ± 4.9%, P < 0.05) as compared to the other two treatment modalities. DSA decreased HDL-cholesterol by -10.4 ± 6.1% and the DALI system by -12.7 ± 5.0%. Remarkable differences were found for the removal of fibrinogen (DSA: -29.8 ± 14.7%, P < 0.05 versus DALI/IMAL; IMAL: -21.4 ± 10.1% (P < 0.05 versus DALI); DALI: -14.8 ± 8.0%). The shortest duration for treatment was achieved by the DALI system (135 ± 20 min, P < 0.05 versus IMAL (195 ± 20 min) and DSA (187 ± 29 min)). No side effects were recorded in the total of 96 treatments performed during the study. Long-term observations have yet to prove whether these differences in efficacy may be of clinical relevance. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: LDL-apheresis; Immunoadsorption; Dextran sulphate adsorption; Direct adsorption of lipoproteins; Cross-over comparison; LDL-cholesterol; Fibrinogen

1. Introduction

The use of LDL-apheresis to treat patients with homozygous or severe heterozygous familial hypercholesterolaemia (FH) has gained wider clinical acceptance during recent years. For this extracorporeal approach, single- and reuse systems with different modes of action are commercially available [1–14]. Metabolic efficacy in all systems has been correlated to reduced progression or even regression of coronary artery disease (CAD). However, this therapeutic procedure is rarely indicated in particular since the introduction of atorvastatin, a new HMG-CoA reductase inhibitor with lipid lowering capacity even in homozygous FH patients [1,15,16]. Methods for selective removal of LDL-cholesterol and Lp(a) include one reusable system: immunoadsorption (IMAL) columns coated with immobilised polyclonal sheep antibodies binding apolipoprotein (Apo) B-100 containing lipoproteins, and three single-use devices. These are the heparin-induced LDL precipitation (HELP), dextran sulfate adsorption (DSA) and a novel device removing

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Table 1
Clinical characteristics of patients with FH maintained on long-term LDL-apheresis treatment

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean ± SD: 51 ± 9, Range: 24.5–65</td>
</tr>
<tr>
<td>Sex</td>
<td>Female: 3, Male: 5</td>
</tr>
<tr>
<td>Primary disease</td>
<td>Homozygous: 3, Heterozygous: 5</td>
</tr>
</tbody>
</table>

Values at study entry (mean ± SD)

- Total cholesterol: 234.3 ± 42.7
- Triglycerides: 128.8 ± 56.5
- LDL-cholesterol: 157.1 ± 49.3
- HDL-cholesterol: 43.5 ± 8.9

Body mass index
Mean ± SD: 24.6 ± 2.4

No. of LDL-apheresis treatments at study entry
Median: 209, Range: 4–326

atherogenic lipoproteins by direct adsorption onto polycrylate-coated polycrylamide from the whole blood.

Due to the different modes of action, efficacy and safety have to be proved comparing commercially available devices. Up to now there are a great number of reports investigating the single types of adsorbers. Only one study has been published evaluating three different circuits (HELP, IMAL, DSA) in a cross-over design [11]. However, it should be emphasised that the number of patients (n = 7) and the comparatively small number of treatments (n = 42) in particular may have limited the conclusions of this study.

We, therefore, prospectively compared three LDL-apheresis devices (IMAL, DSA) including the novel direct adsorption of lipoproteins (DALI) system by a randomised cross-over trial with four consecutive treatments on each system in eight patients with homozygous or heterozygous FH.

2. Methods

2.1. Patients and treatment protocol

As three different commercially available LDL-apheresis procedures are offered at our department, this randomised cross-over study was initiated.

Eight patients with familial hypercholesterolaemia (FH) and inadequate response to dietary restrictions as recommended by the American Heart Association [17] and drug-treatment with atorvastatin (mean 77.5 ± 7.1 mg/d) were investigated. Demographic data are shown in Table 1. All patients were already maintained on LDL-apheresis-treatment prior to study entry. The metabolic parameters of the patients are summarised in Table 2. All patients are diagnosed with CAD with the exception of one homozygous patient maintained on LDL-apheresis at weekly intervals since 14 years of age. Eight patients have carotid artery stenosis and six are suffering from peripheral artery sclerosis.

Patients younger than 18 years and patients treated with angiotensin-converting enzyme (ACE) inhibitors (n = 2) were excluded from this study protocol. Patients who fulfilled inclusion criteria were asked to participate in this randomised trial and all subjects gave informed consent to be studied. Dietary restriction and dosage of lipid lowering drugs remained unchanged for the entire study period (12 weeks). For this, every patient underwent four consecutive treatments at weekly intervals with each of the three LDL-apheresis systems (Immunoadsorption: Therasorb system, Teterow, Germany, (IMAL); Dextran sulphate adsorption, Kanegafuchi, Osaka, Japan, (DSA); direct adsorption of lipoproteins by polycrylate-coated polycrylamide, Fresenius, St. Wendel, Germany, (DALI)). The temporal sequence of the three different systems evaluated was randomly designed.

2.2. Methods

All treatments were performed using a peripheral venous vascular approach. Blood was drawn via a 17-gauge needle at a flow rate of 50–80 ml/min.

Table 2
Lipoprotein levels prior to LDL-apheresis treatment and during LDL-apheresis treatment combined with different statin-therapy

<table>
<thead>
<tr>
<th>n = 8</th>
<th>Total cholesterol (mg/dl)</th>
<th>Triglycerides (mg/dl)</th>
<th>LDL-cholesterol (mg/dl)</th>
<th>HDL-cholesterol (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>374.3 ± 96.0</td>
<td>191.4 ± 97.9</td>
<td>300.0 ± 108.6</td>
<td>34.9 ± 12.3</td>
</tr>
<tr>
<td>2b</td>
<td>285.0 ± 38.2 (P &lt; 0.004)*</td>
<td>161.8 ± 64.3 (NS)*</td>
<td>212.3 ± 40.9 (0.02)*</td>
<td>40.4 ± 5.2 (NS)*</td>
</tr>
<tr>
<td>3c</td>
<td>234.3 ± 42.7 (P &lt; 0.05)**</td>
<td>128.8 ± 56.5 (NS)**</td>
<td>157.1 ± 49.3 (P &lt; 0.04)**</td>
<td>43.5 ± 8.9 (NS)**</td>
</tr>
</tbody>
</table>

a Statin therapy (simvastatin 40 mg/d) before initiation of LDL-apheresis treatment.

b LDL-apheresis and statin therapy (no atorvastatin).

c LDL-apheresis and high dosage atorvastatin.

* P as compared to 1.

** P as compared to 2.
Sodium-heparin (Heparin Immuno, Immuno, Vienna, Austria) was given as a bolus of 4000 IU, followed by a continuous input rate of 1500 IU/h (not exceeding 7000 IU per treatment) and additionally citrate (ACD-A, anticoagulant citrate dextrose, formula A; Baxter, Munich, Germany) was added for anticoagulation for the IMAL system. The ratio of citrate to whole-blood flow was kept at 1:18 (5.5%).

Using the DSA system, anticoagulation was performed by an initial bolus of 4000 IU sodium-heparin and a continuous infusion of 1500 IU per hour.

For the DALI system, 2000 IU of sodium-heparin were administered as a bolus and continuous infusion of ACD-A (5.0%) was administered. In addition, the system was prerinsed with 20,000 IU sodium heparin.

2.3. LDL-apheresis procedures

2.3.1. Immunoadsorption of lipoproteins (IMAL)

For initial plasma separation as required for the IMAL system, the Autopheresis-C therapeutic plasma system (TPS; Baxter, Deerfield, IL) was used as recently described in detail [3,18]. LDL-immunoapheresis was performed in an automated double-needle, continuous-flow operation in which the TPS is connected with an adsorption-desorption automate (Medicap, Düsseldorf, Germany). Two columns containing each 310 ml Sepharose 4B gel, coupled with polyclonal sheep apolipoprotein B-100 antibodies, were used for lipoprotein removal [3,10,18]. In each adsorption cycle 1000 ml plasma were loaded on one column (plasma flow rate: 25–35 ml/min), while the other column was regenerated. A total of six cycles was performed at each immunoadsorption session.

Columns were regenerated by elution of Apo-B containing lipoproteins with glycine buffer at pH 2.8, followed by a subsequent rinse with phosphate-buffered saline (PBS) and 9 g/l isotonic sodium chloride solution. Two columns were assigned to each patient, which were reused and stored under sterile conditions.

2.3.2. Dextran sulfate cellulose adsorption (DSA)

The Kaneka MA 01 monitor (Kaneka Corporation, Osaka, Japan) with a plasma separator (Plasmassflow OP-05W(L), Asahi Medical Co. Ltd., Tokyo, Japan) and dextran-sulfate columns (Liposorber LA-15, Kagafuchi Chemical Industry Co., Ltd., Osaka, Japan) was used [7,13,14,19,20]. This single use system mediates adsorption of atherogenic lipoproteins by cellulose beads covalently linked with dextran sulfate.

2.3.3. Direct adsorption of lipoproteins (DALI)

This single use system offers direct adsorption of atherogenic lipoproteins from whole blood. The elimination of LDL-cholesterol and Lp(a) is mediated by adsorption onto polyacrylate coated polyacrylamide beads as recently described [4–6]. There is an electro-chemical interaction of the cationic groups of apolipoprotein B (ApoB)-containing lipoproteins with polyacrylate-coated polyacrylamide. As all positively charged ions, and thus also serum electrolytes, are bound to the adsorber, the induction of electrolyte derangements must be prevented by flushing the adsorber columns before treatment with a rinsing fluid containing these electrolytes. Due to the reported efficacy of the DALI 750 ml adsorber all treatments evaluated during the study period were done with this device [5,6].

2.4. Laboratory methods

Total cholesterol and triglycerides were measured enzymatically using a commercially available kit (Boehringer Mannheim, Mannheim, Germany). Lipoprotein lipids were measured according to the Lipid Research Clinic’s methods with slight modifications as recently described [3,18]. Very-low-density lipoproteins were removed by ultracentrifugation (d < 1.006 g/ml), LDLs were separated from the infranatant (d < 1.063 g/ml) by heparin and polyanion precipitation using manganese chloride. High-density lipoprotein (HDL)-cholesterol was determined from the supernatant. Lp(a) was determined quantitatively using an enzyme immunoassay (Innotest Lp(a); Innogenetics, Belgium). Apolipoproteins were quantified by radial immunodiffusion.

2.5. Statistical analysis

Values are presented as means ± SD or medians as appropriate. Differences in pre-treatment and post-treatment values between groups were compared by one-way ANOVA followed by Tukey’s multiple range comparison test. Student’s t-test for paired date was used to compare baseline and final values after four consecutive LDL-apheresis treatments as well as for pooled pre- and posttreatment data of four cycles.

3. Results

3.1. Technical aspects

All patients included completed this comparative study of 96 treatments which were evaluated for efficacy and safety in the three treatment modalities. During IMAL (n = 32) a plasma volume of 6000 ± 0 ml was desorbed. For DSA (n = 32) three times the individual plasma volume as calculated from 8% of the body weight (blood volume) and corrected by the haematocrit [19] was processed. The mean plasma volume treated by DSA was 5090 ± 600 ml. In the case of the DALI system (n = 32) 1.6 times the patients’ calculated blood volume [21] was filtered (7171 ± 1329 ml).
Table 3
Changes in lipoproteins by LDL-apheresis treatment

<table>
<thead>
<tr>
<th></th>
<th>n = 8</th>
<th>IMAL</th>
<th>DSA</th>
<th>DALI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total cholesterol</strong> (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td></td>
<td>225.1 ± 54.9</td>
<td>233.5 ± 54.6</td>
<td>241.0 ± 61.2</td>
</tr>
<tr>
<td>Posttreatment*</td>
<td></td>
<td>72.5 ± 18.6</td>
<td>75.4 ± 14.6</td>
<td>94.5 ± 29.0</td>
</tr>
<tr>
<td><strong>Triglycerides</strong> (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td></td>
<td>122.1 ± 66.1</td>
<td>122.3 ± 61.1</td>
<td>119.2 ± 57.4</td>
</tr>
<tr>
<td>Posttreatment*</td>
<td></td>
<td>62.5 ± 35.7</td>
<td>49.3 ± 20.5</td>
<td>73.2 ± 44.8</td>
</tr>
<tr>
<td><strong>LDL-cholesterol</strong> (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td></td>
<td>160.5 ± 44.0</td>
<td>162.0 ± 46.2</td>
<td>173.4 ± 54.0</td>
</tr>
<tr>
<td>Posttreatment*</td>
<td></td>
<td>29.5 ± 15.9</td>
<td>25.0 ± 10.9</td>
<td>44.1 ± 24.2</td>
</tr>
<tr>
<td><strong>HDL-cholesterol</strong> (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td></td>
<td>43.9 ± 8.8</td>
<td>47.5 ± 10.3</td>
<td>46.0 ± 6.0</td>
</tr>
<tr>
<td>Posttreatment*</td>
<td></td>
<td>34.5 ± 6.7</td>
<td>42.3 ± 8.3</td>
<td>40.1 ± 5.2</td>
</tr>
<tr>
<td><strong>Apolipoprotein A1</strong> (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td></td>
<td>122.4 ± 15.1</td>
<td>128.0 ± 20.1</td>
<td>130.5 ± 19.6</td>
</tr>
<tr>
<td>Posttreatment*</td>
<td></td>
<td>88.9 ± 14.7</td>
<td>105.1 ± 14.0</td>
<td>96.7 ± 20.3</td>
</tr>
<tr>
<td><strong>Apolipoprotein B</strong> (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td></td>
<td>119.8 ± 27.4</td>
<td>128.8 ± 31.0</td>
<td>125.5 ± 29.3</td>
</tr>
<tr>
<td>Posttreatment*</td>
<td></td>
<td>31.3 ± 3.3</td>
<td>31.2 ± 3.7</td>
<td>35.6 ± 8.6</td>
</tr>
<tr>
<td><strong>Lp(a)</strong> (mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pretreatment</td>
<td></td>
<td>17.3 ± 10.4</td>
<td>16.5 ± 9.8</td>
<td>16.5 ± 10.1</td>
</tr>
<tr>
<td>Posttreatment*</td>
<td></td>
<td>5.0 ± 4.6</td>
<td>4.9 ± 4.6</td>
<td>5.6 ± 4.8</td>
</tr>
</tbody>
</table>

* Comparison between pre- and posttreatment values; P < 0.001.
** n = 7; one patient with pretreatment Lp(a) levels <3 has been eliminated from this statistic.

Duration of a single treatment differed according to the adsorption device used (IMAL: 195 ± 20 min; DSA: 187 ± 29 min, NS, as compared to IMAL; DALI: 135 ± 20 min, P < 0.05 as compared to IMAL and DSA). No side effects were observed during and following these 96 LDL-apheresis treatments.

3.2. Lipoprotein removal by different LDL-apheresis procedures

The pretreatment LDL-cholesterol values obtained at the initial application were comparable for each LDL-apheresis system (IMAL: 180.9 ± 63.0 mg/dl; DSA: 152.0 ± 42.1 mg/dl; DALI: 160.8 ± 29.1 mg/dl, NS.). No significant change in LDL-cholesterol was observed when pretreatment values after four subsequent procedures were compared (IMAL: 162.4 ± 27.3 mg/dl; DSA: 152.4 ± 23.6 mg/dl, NS; DALI: 176.9 ± 62.3 mg/dl; NS).

For comparison of therapeutic efficacy (reduction in lipoproteins by LDL-apheresis) of the different systems, four treatments with each single device were evaluated. All LDL-apheresis systems provided sufficient removal of Apo-B containing lipoproteins (Table 3). Reduction of LDL-cholesterol obtained in IMAL and DSA were comparable but significantly higher than that achieved by the DALI system (DALI versus IMAL: P < 0.05; DALI versus DSA: P < 0.05).

These detailed values are summarised in Table 3. Percentual reduction for LDL-cholesterol, HDL-cholesterol and Lp(a) are demonstrated in Fig. 1A–C.

Reduction in fibrinogen by LDL-apheresis treatment significantly varied according to the system used (% reduction by LDL-apheresis treatment: IMAL: –21.4 ± 10.1%, from 253.1 ± 42.7 to 198.4 ± 40.5 mg/dl DSA: –29.8 ± 14.7%, 261.1 ± 60.6 to 174.1 ± 51.0 mg/dl; DALI: –14.8 ± 8.0%, from 269.2 ± 51.2 to 225.3 ± 43.2 mg/dl; Fig. 1D).

Fig. 1. Lipoprotein and fibrinogen reduction (%) by three different LDL-apheresis systems: IMAL, immunoadsorption; DSA, dextrane sulphate adsorption; DALI, direct adsorption of lipoproteins. (A) for LDL-cholesterol; (B) for HDL-cholesterol; (C) for Lp(a); (D) for fibrinogen.
During the observation period (4 weeks for each adsorber) no significant changes in haemoglobin concentration, leucocyte- and thrombocyte count was observed.

4. Discussion

Extracorporeal LDL-apheresis is an accepted tool for primary prevention of CAD in patients with homozygous FH and for secondary prevention in severe heterozygous FH [1–3, 7, 10–14, 19, 22–28]. At present four different devices with a different mode of removing lipoproteins are commercially available, three of them (IMAL, DSA, DALI) are in clinical practice at our unit. The decision on which of the three systems a patient will be set on for routine LDL-apheresis treatment is made on the availability of the several devices.

This, to our knowledge, first comparative cross-over study on IMAL, DSA and the DALI system demonstrates that each device was able to therapeutically remove Apo-B containing lipoproteins both in patients with homozygous and severe heterozygous FH.

Nevertheless, a slight but significant lower reduction in LDL-cholesterol for the DALI system was found (Table 3; Fig. 1A) which, however, did not result in an increase in the pretreatment (before LDL-apheresis) LDL-cholesterol levels in particular. Reduction in HDL-cholesterol during LDL-apheresis treatment was significantly higher for the IMAL-system as compared to the DSA and DALI device (Fig. 1B). Reduction in HDL-cholesterol is a common finding in apheresis patients, but this lowering effect is of short duration, as already 24 h after treatment pre-LDL-apheresis values are reached again and long-term treatment results in a significant rise (Table 2) in HDL-cholesterol [1, 3, 5–7, 10–13, 28]. As demonstrated in Table 2 the administration of about 80 mg of atorvastatin was associated with a remarkable decrease in LDL-pretreatment values even though these patients were already on HMG-CoA reductase inhibitor treatment before atorvastatin treatment. Comparable results in homozygous FH patients on LDL-apheresis treatment have already been published [29].

Lp(a) removal by LDL-apheresis was comparable at about 60% for all three different systems used (Fig. 1C). This reduction in Lp(a) is below that reported for LDL-apheresis patients with elevated (>30 mg/dl) Lp(a) values of 72% [3–5, 7]. The lower efficacy of Lp(a) reduction is mainly due to methodological limitations to precisely determine values less than 2 mg/dl as obtained in the serum after LDL-apheresis in patients with low Lp(a) pretreatment values (Lp(a) < 8 mg/dl; n = 3 of 8). A remarkable and significant difference in the removal of fibrinogen due to the device used was found (Fig. 1D). Reduction in fibrinogen was highest for the DSA-system, followed by the IMAL-adsorber and was lowest in DALI treated patients. Fibrinogen lowering during LDL-apheresis has been demonstrated to improve plasma viscosity and red cell aggregation [12, 22]. Thus, in patients with moderately elevated serum fibrinogen the use of the DSA-system might be beneficial for long-term treatment in this respect. However, removal of fibrinogen can be increased by discarding separated plasma prior or at the end of the DSA and IMAL treatment. This combination of plasma exchange (0.9% sodium chloride solution) with LDL-apheresis, performed frequently in our centre, is only possible for those systems necessitating initial plasma separation.

Duration of treatment was comparable for the IMAL- and the DSA-system but significantly shorter for DALI treatments. This advantage in combination with the ease of use of the DALI device which does not necessitate initial plasma separation, might favour the decision for this single-use LDL-adsorber [4–6]. However, the slightly but significantly lower efficacy of the DALI system could be diminished by increasing the treated blood volume, as the 750-adsorber still is efficient in removing lipoproteins at the end of the treatment session [4–6].

Certainly, the cost of LDL-apheresis devices might be different in each centre. At present the lowest price at our department is achieved for the reuse system (IMAL) as the columns are re-used up to 60 times in consecutive treatments. For both single-use devices identical costs for a single treatment have to be calculated.

In general, the reported rate of side effects from the different systems is low as observed in a total of 96 LDL-apheresis treatments within this cross-over study. However, in patients dependent on ACE-inhibitor therapy due to ischaemic myocardial insufficiency, only the IMAL system can be used, as serious bradycardic reactions have been reported for the DALI and DSA circuit [1–8, 10, 11, 13, 14, 19, 28]. Nevertheless, commonly adverse events were only reported as short-term effects (e.g. hypotension, arrhythmias, angina pectoris, headaches, local complications due to the veno-venous approach) and little information is available on long-term effects of particle release by extracorporeal circuits. This microparticle release cannot be entirely avoided in extracorporeal circuits or when using haemofiltration solutions. Inoue and Bambauer reported an increased particle release (95 pieces/ml) from the DALI-750 adsorber during a simulated treatment [30]. This amount of particle release would exceed the acceptable standards set by the United States Pharmacopoeia (USP) and the European Pharmacopoeia (Ph.Eur.). However, this result has been rebutted by Martins et al. at the Congress of the International Society for Apheresis (Saarbrücken, Germany, 1999;
data prepared for publication). Martins et al. reported that particle release obtained for the DALI system was comparable to that of the DSA-system and approximately 90% below the limits required by the USP and Ph.Eur. This difference from the results of Inoue and Bambauer [30] seems to be related to the distinct study design, as only for the second report the original DALI equipment was used. This involves prerinsing of the device which reduces the particle exposure to the patients.

The results of this prospective randomised cross-over investigation demonstrate that each of the three commercially available LDL-apheresis systems, despite differences in the mode of action, are safe and highly effective in removing atherogenic lipoproteins in patients with homozygous or severe heterozygous FH.

Significant differences between the LDL-apheresis single-use systems (DALI and DSA) and the reuse device (IMAL) were found regarding the duration of treatment, reduction of LDL-cholesterol and fibrinogen. To answer the question of whether this slight distinction in efficacy might be of clinical importance, further investigation is required.

References


