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LIPIDS AND CARDIOVASCULAR DISEASE

Apheresis for severe hypercholesterolaemia and elevated lipoprotein(a)

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Summary

Low-density lipoprotein (LDL)-cholesterol (LDL-c) and lipoprotein(a) [Lp(a)] are independent cardiovascular risk factors. Reduction of LDL-c leads to reduction in cardiovascular events, regardless of the method of reducing LDL-c levels. Lifestyle modification and drugs are first line treatment options. However, many patients do not reach treatment goals, as defined in guidelines worldwide, through standard medication. So far, drugs are not efficient in lowering Lp(a) levels, or the reduction of plasma levels does not result in clinical benefit. In these two groups of patients lipoprotein apheresis is very efficient in decreasing LDL-c and Lp(a) levels. A single apheresis session can decrease LDL-c and Lp(a) by approximately 65%, and apheresis performed weekly or biweekly results in considerably decreased mean interval concentrations (approximately 30% reduction). Most apheresis systems (HELP, heparin induced extracorporeal LDL precipitation; DALI, direct adsorption of lipoproteins; lipoprotein apheresis with dextran sulfate; lipid filtration; immunoadsorption) decrease LDL-c and Lp(a). Lipopac is a specific form of immunapheresis and only decreases Lp(a). Lipoprotein apheresis is a well-tolerated treatment option but it is expensive and time consuming. The evidence for clinical benefit through regular apheresis comes from observational data. Adequate, randomised, controlled trials are lacking.

Key words: Apheresis; Lp(a); lipoprotein; LDL; Cholesterol.

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INTRODUCTION

Elevated concentrations of lipoproteins are causally linked to atherosclerosis and cardiovascular disease.[1–4] Therefore, reducing elevated concentrations of lipoproteins is an important strategy in primary and secondary prevention of cardiovascular diseases. Lifestyle modification should be the baseline treatment approach to reduce lipoproteins and other cardiovascular risk factors. In the 1990s, the use of statins as cholesterol lowering medication first showed positive effects on cardiovascular outcome. Nowadays ezetimibe and PCSK9 inhibitors (PCSK9-i) are evidence-based options for add-on lipid lowering therapy.[5–7] Elevated levels of lipoprotein(a) [Lp(a)] cannot be addressed by lifestyle modification. Of the currently available drugs, niacin and PCSK9-i have significant effects on Lp(a) concentrations. However, niacin therapy has not translated into clinical benefit, while the value of PCSK9-i induced Lp(a) reduction is currently unclear.[8,9] Similarly, the role of other lipid modifying drugs in development is currently unclear, such as ANGPTL3 inhibitors,[10–12] apoE mimetic peptides,[13] apoB antisense oligonucleotides, and MTP-inhibitors.[14]

For more than 40 years lipoprotein apheresis has been a therapy of 'last resort' to address dyslipidaemias that can otherwise not be treated. However, the development of new medications has shifted this indication, as more dyslipidaemias than before can be treated without apheresis. In this review we describe the current role of lipoprotein apheresis.

Lipoprotein concentrations can be reduced by extracorporeal elimination or, more specifically, by lipoprotein apheresis. Such procedures were first described as a treatment option for severe hyperlipoproteinaemia [homozygous familial hypercholesterolaemia (FH)] in 1975.[15] More specific techniques to reduce apolipoprotein B (apoB) containing particles such as low-density lipoprotein (LDL)-cholesterol (LDL-c) and Lp(a) were developed in the 1980s.[16,17] With the development of new and less invasive therapeutic options the role of apheresis in the treatment of hyperlipidaemia has shifted.[18–20] Currently, there are five different techniques available to eliminate apolipoprotein B (apoB) containing lipoproteins. In addition, there is one technique that is specific for Lp(a).

In this review we will discuss the indications for apheresis, describe the different techniques and review the current evidence regarding the efficacy and the long-term effect on cardiovascular disease.

PATH TO LIPOPROTEIN APHERESIS

Apheresis for elevated LDL-cholesterol

In most patients with LDL-hypercholesterolaemia (with the exception of some patients with statin intolerance, severe heterozygous FH or homozygous FH) LDL-c goals can be achieved if a combination of lifestyle modification, statins, ezetimibe and PCSK9-i is used (Fig. 1).[21] Until the introduction of PCSK9-i, many patients with FH, especially when statin intolerant, required apheresis to achieve treatment goals. As patients with FH usually respond well to PCSK9-i therapy and PCSK9-i are tolerated well by statin intolerant patients, the introduction of PCSK9-i has reduced the number of patients requiring apheresis for elevated LDL-c dramatically. In one study, the use of PCSK9-i allowed apheresis therapy to be discontinued in 63.4% of patients with heterozygous FH, and

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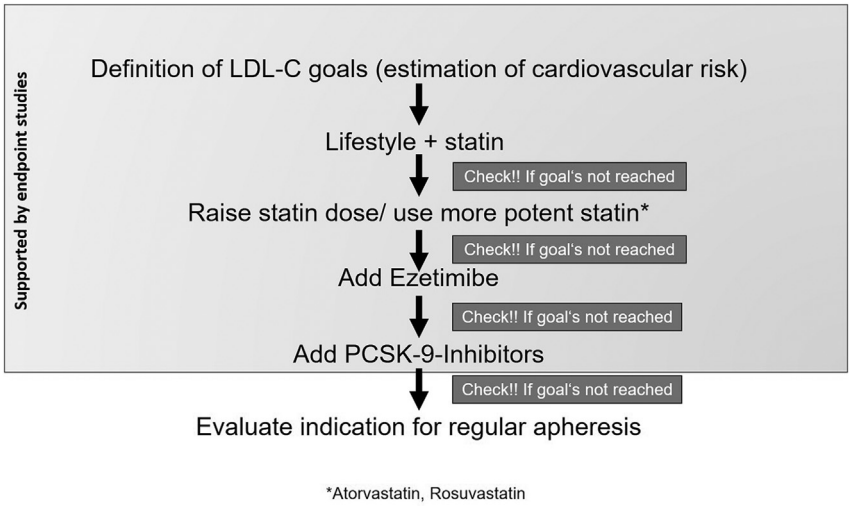

Fig. 1 Path to apheresis in patients with high LDL-c. Adapted from Parhofer.[21]

the interval between treatments to be stretched in a further 30%.[22] However, it must be noted that in this study apheresis was discontinued if pre-apheresis LDL-cholesterol was 30% or more below baseline pre-apheresis LDL-cholesterol (indicating that PCSK9-i were more potent than apheresis in reducing LDL-cholesterol). When reaching treatment target is the goal, then many patients with severe heterozygous FH require both treatment modalities. Similarly, in homozygous FH a less dramatic effect would be expected, as many patients with homozygous FH do not respond as well to PCSK9-i; even if they respond, LDL-cholesterol concentration remains considerably above target.[23,24] In another observational study, post-apheresis LDL-c was comparable to levels during PCSK9-i therapy.[25]

It has long been discussed whether apheresis not only decreases atherogenic lipoproteins, but also has pleiotropic effects by affecting rheologic parameters and removing additional compounds. Thus, apheresis reduces C-reactive protein (CRP) levels in the long-term, while PCSK9-i have no effect on inflammatory parameters.[25,26] However, it is unclear whether this difference is of any clinical significance.

Current indications for apheresis for elevated LDL-c vary considerably by country.[16] In the USA homozygous FH is the main indication for lipoprotein apheresis. It is also approved in forms of severe LDL-hypercholesterolaemia with persistently elevated lipoprotein levels despite maximal drug therapy [LDL >300 mg/dL (7.6 mmol/L) without concomitant cardiovascular disease or >200 mg/dL (5.2 mmol/L) with concomitant cardiovascular disease].[27] These patients are often underdiagnosed and undertreated.[28] In Germany, apheresis for elevated LDL-c can be performed in severe hypercholesterolaemia if LDL-c cannot be reduced sufficiently, despite maximal dietary and drug therapy (documented for 12 months). No specific threshold is given because the overall risk profile of the patient should be considered in evaluating the indication for apheresis. However German authorities require that PCSK9-i are given before the patient is evaluated for apheresis. Other countries have less specific recommendations with respect to apheresis for elevated LDL-c.[16,29,30] Generally, homozygous FH is widely recognised as an indication, while other forms of LDL-hypercholesterolaemia are not.

Apheresis for elevated lipoprotein(a)

Lp(a) is an apo(B)-containing lipoprotein similar to LDL with an additional apoprotein apo(a). It is causally linked to atherosclerotic disease and has gained increasing recognition as a cardiovascular risk factor in recent years. From a lipidologist's point of view Lp(a) is a particularly atherogenic LDL particle which is generally not catabolised via the LDL-receptor and therefore has a longer half-life in plasma. Lp(a) concentrations are mainly genetically determined and around 20% of the population have elevated levels above 50 mg/dL.[31]

Apheresis can decrease the concentration of all apoB containing lipoproteins. Therefore, Lp(a) concentrations are decreased to a similar extent as LDL concentrations. Furthermore, regular apheresis treatment leads to a reduction in pre-apheresis Lp(a) concentrations. As the role of Lp(a) in atherosclerosis is less well defined, the role of apheresis in the treatment of elevated Lp(a) is much less clear compared to its role in treating LDL-hypercholesterolaemia.

While it is widely recognised that Lp(a) concentrations can be decreased with apheresis, only in Germany are isolated elevated Lp(a) levels considered to be an indication for regular apheresis in certain patients. Such treatment is reimbursed by health insurers if certain prerequisites are fulfilled (Fig. 2). According to German guidelines, apheresis may be indicated if Lp(a) is >60 mg/dL (0.6 g/L) in patients with progressive cardiovascular disease despite optimal management of all other risk factors including LDL-c; either clinical progression or progression documented with imaging techniques is mandatory.[32]

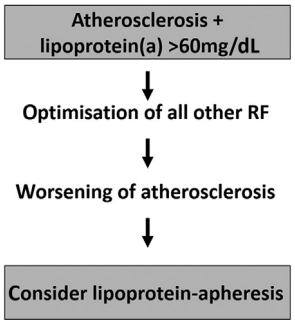

Fig. 2 Path to apheresis in patients with elevated Lp(a). RF, risk factors.

The National Lipid Association Expert Panel on Familial Hypercholesterolaemia recommends apheresis in functional heterozygotes with LDL-c >200 mg/dL (5.2 mmol/L) [or non-high density lipoprotein (HDL)-c >230 mg/dL (5.9 mmol/L)] and additional risk factors, including elevated Lp(a) >50 mg/dL (0.5 g/L), although the US Food and Drug Administration (FDA) does not comment on apheresis for isolated elevated Lp(a).[33] Similarly, the HEART-UK criteria for the use of LDL apheresis include patients with progressive coronary artery disease, hypercholesterolaemia, and Lp(a) >60 mg/dL (0.6 g/L) in whom LDL-c remains elevated despite drug therapy.[29]

In summary, Germany is the only country where apheresis may be considered for isolated Lp(a) elevation. Other countries and international guidelines take elevated Lp(a) as an additional risk factor into account when apheresis is considered for the treatment of LDL-hypercholesterolaemia.

As new drugs are being developed that either specifically address elevated Lp(a) levels [such as apo(a) antisense-oligonucleotides] or that modify a number of different lipoproteins, including Lp(a), indications for apheresis may change in coming years.

Procedures

Observational data on lipoprotein apheresis favours regular treatment every week or every two weeks independent of the indication for treatment [elevated LDL and/or elevated Lp(a)]. The length of an individual apheresis session depends on the plasma volume to be treated (usually reflecting pre-apheresis lipoprotein concentrations) and varies between 1.5 and 4 hours per session. The main vascular approach for all apheresis techniques is veno-venous. Only very few patients need shunt surgery. Some form of anticoagulation is mandatory for every apheresis system. A blood volume of approximately 500 mL circulates extracorporeally. This can result in a drop in blood pressure. Anaemia and iron deficiency are other associated side effects in some patients and may necessitate iron substitution if apheresis is conducted on a regular basis. However, generally speaking, all apheresis methods are tolerated well, and patients connected to specialised centres usually show very good compliance. Adherence to and compliance with regular therapy may also depend on costs and funding of the procedure.[34]

The different principles underlying the different apheresis systems are shown in Fig. 3.

Heparin-induced extracorporeal LDL-precipitation (HELP)

HELP was first introduced in the 1980s.[35] ApoB containing lipoproteins [including LDL and Lp(a)] which form complexes with a number of other proteins (e.g., CRP and fibrinogen) in an acidic environment (pH 5.12) are thereby precipitated and then eliminated. This procedure simultaneously eliminates fibrinogen. This may be seen as an advantage (although the causal role of fibrinogen for cardiovascular events is disputable) but also limits the amount of plasma that can be treated in one session.

Direct adsorption of lipoproteins (DALI)

DALI was the first whole blood system implemented in 1996.[36] Positively charged apoB binds to negatively charged polyacrylate ions bound to a column, thereby all apoB containing lipoproteins are eliminated. Angiotensin-converting enzyme (ACE) inhibitor therapy is contra-indicated because bradykinin released during apheresis with DALI is normally inactivated by the ACE. While concurrent therapy ACE inhibitors may lead to severe hypotension, angiotensin receptor antagonists can be given safely.

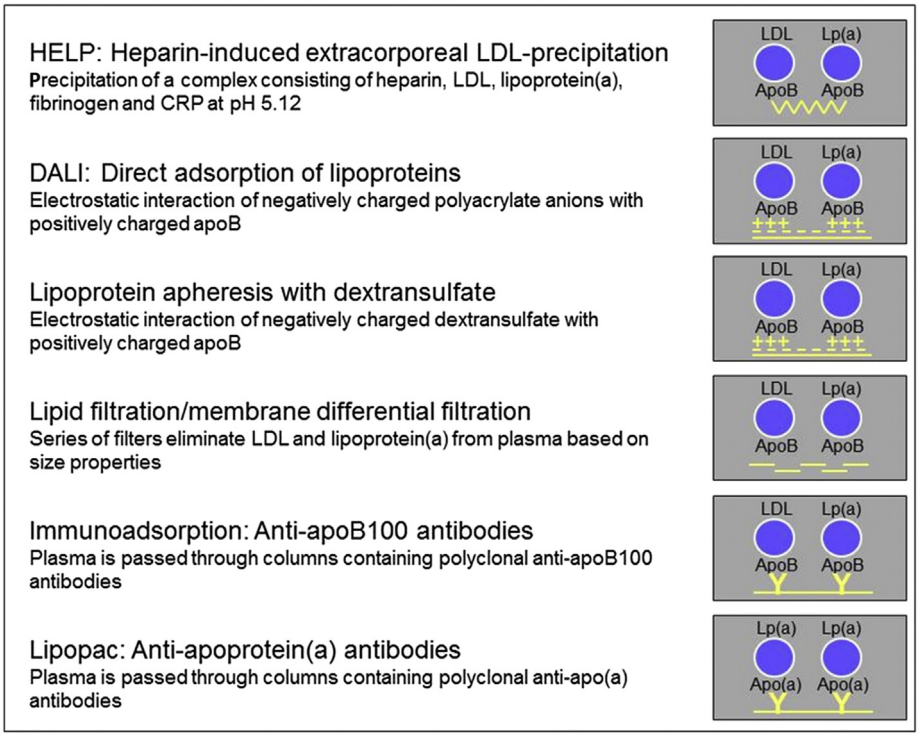

Fig. 3 Apheresis systems for eliminating LDL-c and/or Lp(a). Adapted from Waldmann and Parhofer.[58]

Apheresis with dextran sulfate (Kaneka)

This similarly uses a negative electric charge (cellulose-bound dextran sulfate) to eliminate apoB-100 containing lipoproteins which include LDL, intermediate-density lipoprotein (IDL), and very low-density lipoprotein (VLDL), as well as Lp(a).[37] Similarly, as discussed above for DALI, apheresis with dextran sulfate cannot be combined with ACE inhibitor therapy, while angiotensin receptor therapy is safe.

Lipid filtration/membrane differential filtration (OctoNova, Diamed; Evaflux, Kawasumi)

Also called cascade filtration, this technique is based on the elimination of particles by size. Filters of such size that only LDL, Lp(a) and fibrinogen are held back are connected in series.[38] The remaining plasma components pass the filter without being eliminated. Obviously, this method requires separation of plasma from cellular components of blood beforehand. Again, ACE inhibitor therapy cannot be used concomitantly.

Immunapheresis or immunadsorption

This was one of the first apheresis techniques to be developed.[17] Sheep antibodies against apoB bound to columns are used to eliminate apoB-100 containing particles such as LDL, IDL and Lp(a). VLDL are largely protected against elimination because the epitopes on apoB interacting with the antibodies are protected by lipids. Since the mechanism is very specific for apoB-100-containing particles there is no relevant elimination of other plasma components. This allows treatment of very large plasma volumes without eliminating other proteins or particles.

Lipopac apheresis

Lipopac is another form of immunapheresis introduced in 1994.[39] In contrast to immunoadsorption (antibodies against apoB) the antibodies are directed specifically against apolipoprotein(a). Plasma is passed through columns loaded with sheep polyclonal monospecific antibodies against human apolipoprotein(a). Besides Lp(a) no other lipoproteins are affected.

However, to the authors of this article it is unclear whether an apheresis method which only reduces Lp(a) offers any advantage over methods reducing Lp(a) and LDL-c. The studies using PCSK9-i have shown no safety signal even for very low LDL-c levels. In contrast, the lower the LDL-c level, the bigger the benefit. Thus, it seems reasonable to use an apheresis method that decreases Lp(a) and LDL-cholesterol even if Lp(a) is the primary indication for apheresis.

EFFECT OF LIPOPROTEIN APHERESIS ON LIPID LEVELS

Despite the differences in the underlying methodology, all apheresis systems affect lipoprotein levels to a similar extent.[11,16,30–35,40–45] In general the extent of the acute lipoprotein reduction is a function of the plasma volumes treated during an apheresis. Therefore, the length of a session has impact on the effect on lipoprotein levels. LDL and Lp(a) decrease by approximately 60–65% with each apheresis treatment [Lipopac, as a Lp(a)-specific system, has very little effect on LDL-c]. It should also be noted that with weekly apheresis, pre-apheresis Lp(a) values decrease over time since the rebound of Lp(a) concentration is not sufficient to achieve baseline values within one week, a phenomenon which is much less relevant for LDL-c. Depending on the selected interval (weekly or biweekly) and baseline concentration, mean interval reduction of LDL-c and Lp(a) varies between 20% (biweekly apheresis, relatively low baseline values)[42] and 36% (weekly apheresis, high baseline values).[43] Even in patients with Lp(a) as a leading risk factor and LDL-c levels at target it seems tempting to use non-specific apheresis systems leading to lower Lp(a) concentrations and 'really low' LDL-c levels. Considering what we have learnt from the PCSK9-i studies there seems no reason to believe that isolated Lp(a) reduction is better than lowering Lp(a) and LDL simultaneously (assuming the safety signals remain as they are and that costs for all apheresis systems are similar).

Triglycerides also decrease (up to 50%) but rebound quickly. Similarly, HDL-c can be transiently decreased by 5–10%. The change in HDL has long been seen as a dilution phenomenon but newer data indicate that apheresis (elimination of a significant pool of apoB containing lipoproteins) also directly affects the metabolism of HDL particles.[46]

A series of turnover experiments evaluated whether apheresis acutely or in the long-term affects the endogenous production or catabolism of apoB containing lipoproteins, which is not the case.

The clinical importance of elimination of other proteins by apheresis systems remains unclear. However, even after many years of treatment, there seems to be no specific side effects relating to the elimination of these proteins.

THE EFFECT OF APHERESIS ON ATHEROSCLEROSIS

The goal of apheresis is to decrease the concentration of atherogenic lipoproteins and thereby reduce the risk for cardiovascular events. Although a number of studies have evaluated the effect of apheresis on lipid values, no adequately controlled and powered trial has been performed to test the hypothesis that apheresis results in reduced cardiovascular morbidity or mortality. However, there are a number of studies evaluating potential benefits of apheresis.[6,20,42–45,47–50]

In a non-randomised trial [130 heterozygous FH patients with documented coronary heart disease (CHD)] it was shown that patients on regular apheresis and statin therapy had lower LDL-c values and less cardiovascular events than the control group treated by drug therapy alone.[51] In 2017 Ezhov *et al*. conducted a 12-month interventional study on 50 patients with LDL-c values of >2.6 mmol/L (>100 mg/dL) prior to coronary artery bypass grafting (CABG) surgery despite statin therapy. It was shown that significantly less vein graft occlusions (14.3% vs 27.4%) and progression of atherosclerosis occurred in patients treated with apheresis instead of statin treatment alone for the first year after coronary artery bypass. There were even signs of regression in the apheresis group. In this study LDL-c and Lp(a) were acutely reduced by 59±14% and 49±15%, respectively.[52]

Another trial evaluated whether in patients with heterozygous FH and CHD (n=39), biweekly apheresis in combination with simvastatin (40 mg/day) was superior to simvastatin (40 mg/

day) in combination with colestipol (20 g/day).[53] After 2.1 years there was no significant difference in angiographic changes between the two groups. The authors concluded that 'decreasing Lp(a) seems to be unnecessary if LDL-c is reduced to 3.4 mmol/L or less'. As the study did not select patients with elevated Lp(a) concentrations, it was limited by a low baseline Lp(a) concentration (43 mg/dL) and only a modest Lp(a) reduction with apheresis (mean interval concentration 33 mg/dL) due to the biweekly apheresis interval.

Finally, an angiographic trial evaluated whether atorvastatin together with specific Lp(a) apheresis (Lipopac apheresis) reduced CHD progression compared to atorvastatin alone in patients (n=30) with CHD and elevated Lp(a) (>50 mg/dL).[54] After 18 months, patients treated with atorvastatin and apheresis compared to atorvastatin alone showed significantly more regression and less progression. Again, the trial was limited by a small number of subjects and the lack of reporting of clinical events.

Recently, a first analysis of the German Lipoprotein Apheresis Registry between 2012 and 2015 was reported.[49] It showed acute reductions of LDL-c and Lp(a) by 68.6% and 70.4%, respectively. When the event rate before initiation of apheresis was compared to the event rate during apheresis, major cardiovascular events were reduced by 97%. This very impressive event reduction must be interpreted with caution as the setting was not randomised or controlled. Side effects occurred in only 5%. Another publication showed significant reduction of interventions in patients with peripheral artery disease after initiation of apheresis (observational data).[48]

This recent analysis confirms three previous German evaluations with partially overlapping patient cohorts and an Italian study evaluating cardiovascular event rates before initiation of apheresis and during regular apheresis therapy.[50,55–57] In two of the German studies, only subjects with isolated Lp(a) elevation were included (LDL<2.5 mmol/L on statin therapy),[55,56] while in the third study subjects with concomitantly elevated LDL-c were also incuded.[57]

All four studies show a dramatic decrease in the event rate after initiation of regular apheresis. However, these evaluations are limited by the lack of a control group. Progression of disease and thus recurrence of events is the main reason for initiating apheresis. Therefore, it is not surprising to observe a very high event rate in the period preceding the initiation of apheresis. As outlined elsewhere it is impossible to determine the true effect of apheresis without an adequate control group.[58]

Retrospective analyses are hypothesis-generating in that they indicate that regular apheresis for elevated lipoproteins, Lp(a) as well as LDL-c, may reduce cardiovascular events and modulate progression of atherosclerosis. However, adequately powered and randomised controlled trials are still necessary to give well-grounded evidence for clinical benefit through regular apheresis treatment.

CONCLUSION

Regular apheresis leads to an acute decrease in lipoprotein concentrations by approximately 60–65%, which translates into significant interval mean reduction (25–40%). The treatment is tolerated well with minimal side effects, although costs and time must be taken into account. Retrospective data indicate clinical benefit in patients undergoing regular apheresis therapy, but adequate, randomised controlled trials are lacking. Since PCSK9-i are very potent LDL-c lowering drugs and also decrease Lp(a), the future role of apheresis remains to be determined.

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References

1. Kamstrup PR, Tybjaerg-Hansen A, Steffensen R, *et al*. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA* 2009; 301: 2331–9.
2. Kamstrup PR, Benn M, Tybjaerg-Hansen A, *et al*. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population. The Copenhagen city heart study. *Circulation* 2008; 117: 176–84.
3. Clarke R, Peden JF, Hopewell JC, *et al*. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. *N Engl J Med* 2009; 361: 2518–28.
4. Catapano AL, Graham I, De Backer G, *et al*. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. (Polish.). *Kardiol Pol* 2016; 74: 1234–318.
5. Cannon CP, Blazing MA, Giugliano RP, *et al*. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015; 372: 2387–97.
6. Sabatine MS, Giugliano RP, Keech AC, *et al*. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017; 376: 1713–22.
7. Schwartz GG, Steg PG, Szarek M, *et al*. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018; 379: 2097–107.
8. Boden WE, Probstfield JL, Anderson T, *et al*. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011; 365: 2255–67.
9. Landray MJ, Haynes R, Hopewell JC, *et al*. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med* 2014; 371: 203–12.
10. Dewey FE, Gusarova V, Dunbar RL, *et al*. Genetic and pharmacologic inactivation of ANGPTL3 and cardiovascular disease. *N Engl J Med* 2017; 377: 211–21.
11. Gaudet D, Gipe DA, Pordy R, *et al*. ANGPTL3 inhibition in homozygous familial hypercholesterolemia. *N Engl J Med* 2017; 377: 296–7.
12. Graham MJ, Lee RG, Brandt TA, *et al*. Cardiovascular and metabolic effects of ANGPTL3 antisense oligonucleotides. *N Engl J Med* 2017; 377: 222–32.
13. Anantharamaiah GM, Garber DW, Goldberg D, *et al*. Novel fatty acyl apoE mimetic peptides have increased potency to reduce plasma cholesterol in mice and macaques. *J Lipid Res* 2018; 59: 2075–83.
14. Parhofer KG. New approaches to address dyslipidemia. *Curr Opin Lipidol* 2017; 28: 452–7.
15. Thompson GR, Lowenthal R, Myant NB. Plasma exchange in the management of homozygous familial hypercholesterolaemia. *Lancet* 1975; 1: 1208–11.
16. Thompson GR, Catapano A, Saheb S, *et al*. Severe hypercholesterolaemia. Therapeutic goals and eligibility criteria for LDL apheresis in Europe. *Curr Opin Lipidol* 2010; 21: 492–8.
17. Stoffel W, Borberg H, Greve V. Application of specific extracorporeal removal of low density lipoprotein in familial hypercholesterolaemia. *Lancet* 1981; 2: 1005–7.
18. Sachais BS, Shaz BH. Apheresis to mitigate atherosclerotic vascular disease. *Am J Hypertens* 2018; 31: 945–9.
19. Vogt A. Lipoprotein(a)-apheresis in the light of new drug developments. *Atheroscler Suppl* 2017; 30: 38–43.

20. Wu MD, Moccetti F, Brown E, *et al*. Lipoprotein apheresis acutely reverses coronary microvascular dysfunction in patients with severe hypercholesterolemia. *JACC Cardiovasc Imag* 2018; Jun 9: (Epub ahead of print).
21. Parhofer KG. The treatment of disorders of lipid metabolism. *Dtsch Arztebl Int* 2016; 113: 261–8.
22. Moriarty PM, Parhofer KG, Babirak SP, *et al*. Alirocumab in patients with heterozygous familial hypercholesterolaemia undergoing lipoprotein apheresis. The ODYSSEY ESCAPE trial. *Eur Heart J* 2016; 37: 3588–95.
23. Raal FJ, Honarpour N, Blom DJ, *et al*. Inhibition of PCSK9 with evolocumab in homozygous familial hypercholesterolaemia (TESLA Part B). A randomised, double-blind, placebo-controlled trial. *Lancet* 2015; 385: 341–50.
24. Stein EA, Honarpour N, Wasserman SM, *et al*. Effect of the proprotein convertase subtilisin/kexin 9 monoclonal antibody, AMG 145, in homozygous familial hypercholesterolemia. *Circulation* 2013; 128: 2113–20.
25. Zenti MG, Altomari A, Lupo MG, *et al*. From lipoprotein apheresis to proprotein convertase subtilisin/kexin type 9 inhibitors. Impact on low-density lipoprotein cholesterol and C-reactive protein levels in cardiovascular disease patients. *Eur J Prevent Cardiol* 2018; 25: 1843–51.
26. Otto C, Geiss HC, Empen K, *et al*. Long-term reduction of C-reactive protein concentration by regular LDL apheresis. *Atherosclerosis* 2004; 174: 151–6.
27. Winters JL. Lipid apheresis, indications, and principles. *J Clin Apher* 2011; 26: 269–75.
28. Nordestgaard BG, Chapman MJ, Humphries SE, *et al*. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population. Guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J* 2013; 34. 3478-90a.
29. Thompson GR. Recommendations for the use of LDL apheresis. *Atherosclerosis* 2008; 198: 247–55.
30. Agence Francaise de Securite Sanitaire des Produits de Sante. *Prise en Charge Thérapeutique du Patient Dyslipidémique. (French.)*. 2000; cited 1 Mar 2016. http://www.soc-nephrologie.org/PDF/enephro/recommandations/Afssaps/2005/dyslipemie_argu.pdf
31. Nordestgaard BG, Langsted A. Lipoprotein (a) as a cause of cardiovascular disease. Insights from epidemiology, genetics, and biology. *J Lipid Res* 2016; 57: 1953–75.
32. Gemeinsamer Bundesausschuss. *Richtlinie des Gemeinsamen Bundesausschusses zu Untersuchungs- und Behandlungsmethoden der vertragsärztlichen Versorgung. (German.)*. 2015; cited 1 Mar 2016. https://www.g-ba.de/downloads/62-492-1022/MVV-RL_2015-02-19_iK-2016-05-16.pdf
33. Goldberg AC, Hopkins PN, Toth PP, *et al*. Familial hypercholesterolemia. Screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National lipid association expert panel on familial hypercholesterolemia. *J Clin Lipidol* 2011; 5: 133–40.
34. Khoo KL, Page MM, Liew YM, *et al*. Ten years of lipoprotein apheresis for familial hypercholesterolemia in Malaysia. A creative approach by a cardiologist in a developing country. *J Clin Lipidol* 2016; 10: 1188–94.
35. Armstrong VW, Windisch M, Wieland H, *et al*. Selective continuous extracorporal elimination of low-density lipoproteins with heparin at acidic pH. *Trans Am Soc Artif Intern Organs* 1983; 29: 323–8.
36. Bosch T, Schmidt B, Kleophas W, *et al*. LDL hemoperfusion—a new procedure for LDL apheresis. First clinical application of an LDL adsorber compatible with human whole blood. *Artif Organs* 1997; 21: 977–82.
37. Yokoyama S, Hayashi R, Kikkawa T, *et al*. Specific sorbent of apolipoprotein B-containing lipoproteins for plasmapheresis. Characterization and experimental use in hypercholesterolemic rabbits. *Arteriosclerosis* 1984; 4: 276–82.
38. Matsuda Y, Sueoka A, Nosé Y. An effective LDL removal filter for the treatment of hyperlipidemia. *Artif Organs* 1995; 19: 129–34.
39. Pokrovsky SN, Adamova I, Afanasieva OY, *et al*. Immunosorbent for selective removal of lipoprotein (a) from human plasma. In vitro study. *Artif Organs* 1991; 15: 136–40.
40. Parhofer KG, Geiss HC, Schwandt P. Efficacy of different low-density lipoprotein apheresis methods. *Ther Apher* 2000; 4: 382–5.
41. Otto C, Kern P, Bambauer R, *et al*. Efficacy and safety of a new whole-blood low-density lipoprotein apheresis system (Liposorber D) in severe hypercholesterolemia. *Artif Organs* 2003; 27: 1116–22.
42. Julius U. Lipoprotein apheresis in the management of severe hypercholesterolemia and of elevation of lipoprotein(a). Current perspectives and patient selection. *Med Dev* 2016; 9: 349–60.
43. Julius U, Fischer S, Schatz U, *et al*. Why an apheresis center should offer more than one lipoprotein apheresis method. *Ther Apher Dial* 2013; 17: 179–84.
44. Julius U, Siegert G, Kostka H, *et al*. Effects of different lipoprotein apheresis methods on serum protein levels. *Atheroscler Suppl* 2015; 18: 95–102.
45. Julus U, Metzler W, Pietzsch J, *et al*. Intraindividual comparison of two extracorporeal LDL apheresis methods. Lipidfiltration and HELP. *Int J Artif Organs* 2002; 25: 1180–8.
46. Moriarty PM, Vaisar T, Dutton J, *et al*. The change in HDL proteomics following lipid apheresis therapy. *Eur Heart J* 2018; 39 (Suppl): 1107–8.
47. Julius U, Milton M, Stoellner D, *et al*. Effects of lipoprotein apheresis on PCSK9 levels. *Atheroscler Suppl* 2015; 18: 180–6.
48. Poller WC, Berger A, Dreger H, *et al*. Lipoprotein apheresis in patients with peripheral artery disease and lipoprotein(a)-hyperlipoproteinemia. 2-year follow-up of a prospective single center study. *Atheroscler Suppl* 2017; 30: 174–9.
49. Schettler VJJ, Neumann CL, Peter C, *et al*. Current insights into the German lipoprotein apheresis Registry (GLAR) – almost 5 years on. *Atheroscler Suppl* 2017; 30: 50–5.
50. Bigazzi F, Sbrana F, Berretti D, *et al*. Reduced incidence of cardiovascular events in hyper-Lp(a) patients on lipoprotein apheresis. The GILA (Gruppo Interdisciplinare Aferesi Lipoproteica) pilot study. *Transfus Apher Sci* 2018; Aug 1: (Epub ahead of print).
51. Mabuchi H, Koizumi J, Shimizu M, *et al*. Long-term efficacy of low-density lipoprotein apheresis on coronary heart disease in familial hypercholesterolemia. Hokuriku-FH-LDL-Apheresis Study Group. *Am J Cardiol* 1998; 82: 1489–95.
52. Ezhov MV, Afanasieva OI, Il'ina LN, *et al*. Association of lipoprotein(a) level with short- and long-term outcomes after CABG. The role of lipoprotein apheresis. *Atheroscler Suppl* 2017; 30: 187–92.
53. Thompson GR, Maher VM, Matthews S, *et al*. Familial Hypercholesterolaemia Regression Study. A randomised trial of low-density-lipoprotein apheresis. *Lancet* 1995; 345: 811–6.
54. Safarova MS, Ezhov MV, Afanasieva OI, *et al*. Effect of specific lipoprotein(a) apheresis on coronary atherosclerosis regression assessed by quantitative coronary angiography. *Atheroscler Suppl* 2013; 14: 93–9.
55. Leebmann J, Roeseler E, Julius U, *et al*. Lipoprotein apheresis in patients with maximally tolerated lipid-lowering therapy, lipoprotein(a)-hyperlipoproteinemia, and progressive cardiovascular disease. Prospective observational multicenter study. *Circulation* 2013; 128: 2567–76.
56. Rosada A, Kassner U, Vogt A, *et al*. Does regular lipid apheresis in patients with isolated elevated lipoprotein(a) levels reduce the incidence of cardiovascular events? *Artif Organs* 2014; 38: 135–41.
57. Jaeger BR, Richter Y, Nagel D, *et al*. Longitudinal cohort study on the effectiveness of lipid apheresis treatment to reduce high lipoprotein(a) levels and prevent major adverse coronary events. *Nat Clin Pract Cardiovasc Med* 2009; 6: 229–39.
58. Waldmann E, Parhofer KG. Lipoprotein apheresis to treat elevated lipoprotein (a). *J Lipid Res* 2016; 57: 1751–7.