

V.1 Haemodialysis and prevention of system clotting

Guideline V.1.1

A. To prevent clotting in the extracorporeal circuit during haemodialysis, anticoagulant/antithrombotic treatment is mandatory.

Guideline V.1.2

**A. Differences in thrombogenicity should be considered in the choice of the dialyzer.
(Evidence level: B)**

Commentary on Guidelines V.1.1 and V.1.2

It has been demonstrated in several studies that pre-dialysis concentrations of coagulation proteins such as thrombomodulin and thrombin–antithrombin (TAT) complex can be elevated suggesting hypercoagulability

[3,4]. In most studies on the effect of haemodialysis with different membranes on activation of the coagulation cascade, it was demonstrated that haemodialysis with regenerated cellulose membranes (cuprophane) resulted in more activation of coagulation than haemodialysis with membranes of more recently developed material [4–7]. Sultan *et al.* [8] demonstrated that polyacrylonitrile activated the coagulation pathway to the same extent as cuprophane, whereas Seyfert *et al.* [5] did not. Two other studies found that the polyacrylonitrile membrane induced more coagulation than a cellulose acetate membrane [9] and a polyamide membrane [10]. In at least two studies, it was reported that TAT did not increase during haemodialysis with a polysulfone membrane [4,11]. Greiber *et al.* [12] compared haemodialysis with haemophan filters with polysulphone filters during anticoagulation with low-molecular weight heparin (LMWH). In this study, no clinically relevant clotting was observed, but slightly more fibrin deposition was found in the haemophan filters. For details on membranes and biocompatibility see Section III.

In addition to activation of the clotting cascade, platelets become activated after contact with the extracorporeal circuit. This results in exposure of procoagulant anionic lipids on the platelet surface creating a surface strongly favouring the activation of the factors of the intrinsic coagulation cascade. Furthermore, factor V and trace amounts of prothrombin are released from the platelet granules resulting in a further enhancement of coagulation. In at least two studies it could be demonstrated that cuprophane dialyzers resulted in more platelet activation than other dialyzers [2,5] although this was not confirmed in one [8]. Whereas in one study platelet activation was observed after haemodialysis with a polyacrylonitrile membrane [8], in three other studies this membrane had no significant effect on platelet activation [13,14]. Likewise, in the studies investigating polysulfone membranes either no [11,13,14] or only modest [2] platelet activation was observed.

Summarizing, it can be concluded that blood contact with dialyzers can cause activation of the coagulation cascade and platelet activation. This is especially seen with cuprophane dialyzers and to a lesser extent with other membranes. Thus, to prevent clotting in the extracorporeal circuit during haemodialysis, anticoagulant/antithrombotic treatment is mandatory.

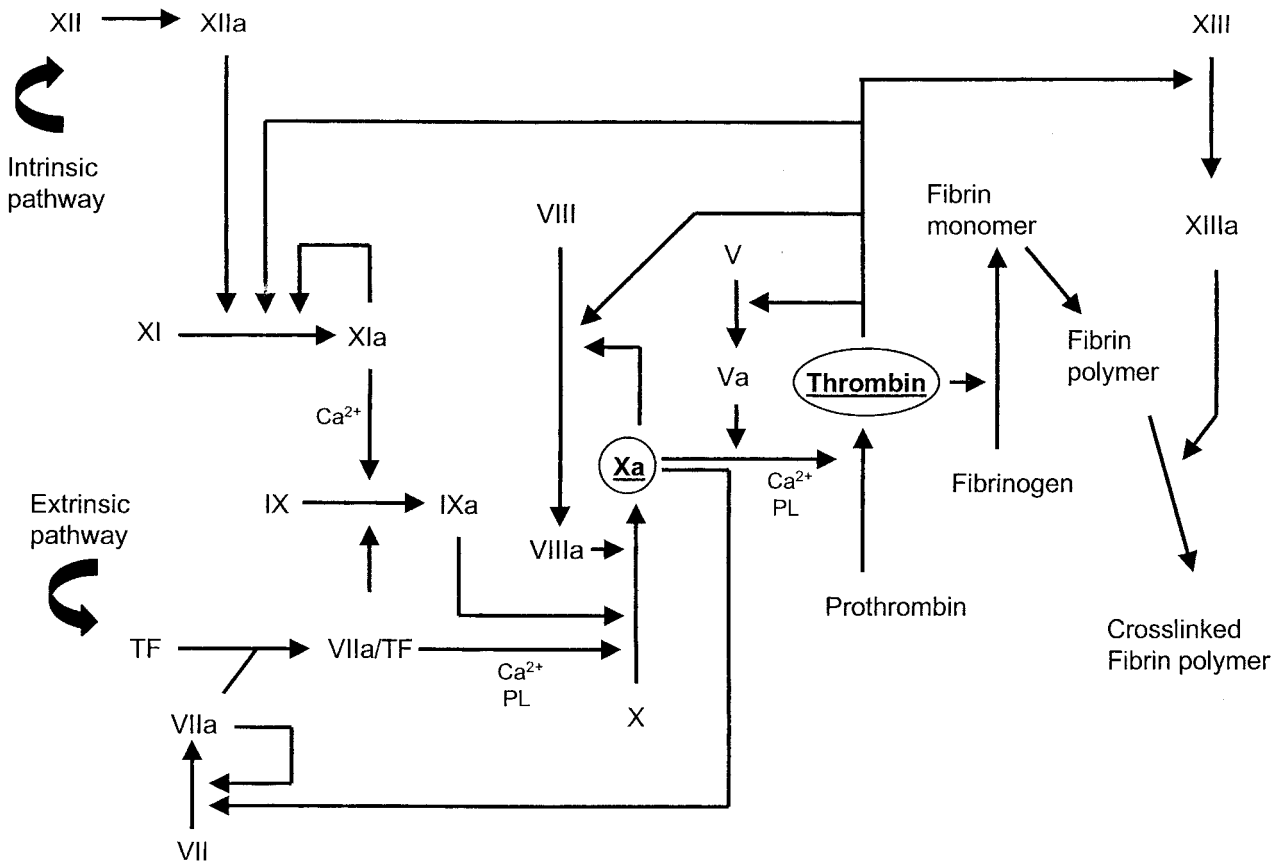


Fig. 1. Overview of the coagulation cascade (PL = phospholipid).

V.2 Prevention of clotting in the HD patient with normal bleeding risk

Guideline V.2.1

A. In patients without elevated bleeding risk low-dose unfractionated heparin or LMWH can be used to prevent clotting of the extracorporeal system during haemodialysis.

(Evidence level: A)

Guideline V.2.2

A. Because of proven safety (evidence level: A), equal efficacy (evidence level: A), and easy handling (evidence level: C) the use of LMWHs is to be preferred over unfractionated heparin. Other benefits of LMWH are an improved lipid profile (evidence level B), less hyperkalaemia (evidence level: B) and less blood loss (Evidence level: C).

Commentary on Guideline V.2.1

Unfractionated heparin

Unfractionated heparin binds to the heparin-binding site of antithrombin-III (AT-III). This induces

conformational changes of AT-III resulting in the transition of AT-III from a slow into a rapid inactivator of clotting factors such as factor Xa and to a lesser extent XIIa, Xia, and IXa. In addition, heparin is an indirect inhibitor of thrombin, for which simultaneous binding of AT-III and thrombin is mandatory. This requires lengths of heparin molecules exceeding 18 monosaccharide units.

At present, routine anticoagulation with heparin is performed with low-dose heparin. Heparin (half-life of ± 1.5 h) can be best given by administration of a loading dose (approximately 50 IU/kg), followed by continuous infusion (800–1500 IU/h) [15–20].

The efficacy of heparin treatment can be evaluated by measurement of the activated partial thromboplastin time or the whole-blood clotting time. A prolongation of the APTT or whole-blood clotting time to 150% of their pre-dialysis values is recommended [20]. Individual dosing schedules can reduce bleeding complications [21–23], but this usually requires mathematic modelling which is inconvenient. Opatrny *et al.* [24] performed a randomly prospective study in which they investigated the effect of rinsing the dialyzer with saline with or without heparin, and comparing low-flux and high-flux polysulfone dialyzers. Blood was sampled at the haemodialyzer inlet before haemodialysis and at 15, 60, and 240 min of haemodialysis. No difference in activation of the coagulation cascade

or platelets could be found between dialysis with or without pre-rinsing with heparin and irrespective of the type of dialyzer used [24]. In addition, no differences in the amount of residual blood volume were found after the respective dialysis sessions. Likewise, in another study no beneficial effect of pre-rinsing with albumin could be found on coagulation or platelet activation using cellulose acetate membranes [25].

In several reports, it has been demonstrated that the use of erythropoietin, with its consequent increase in haemoglobin and haematocrit, results in a greater heparin dose to avoid clotting in the dialyzer [26–30]. Thus, when patients are initiated on haemodialysis with low haematocrits, care should be given to adjust heparin dosage (up to 25%) to achieve appropriate anticoagulation. The few studies that have investigated the effects of different dialyzers on the anticoagulatory efficacy of heparin demonstrated no [15,31] or a limited effect of the dialyzer on heparin dosing [6].

In case of overdosing or active bleeding after heparin administration, the effect of unfractionated heparin can be counteracted by the i.v. administration of protamine (1 mg protamine neutralizes 90–115 USP U heparin; for dosing details see package insert).

At present it can be advised for patients already using agents that affect clotting (i.e. acetylsalicylic acid or coumarins) that the dose of heparin be reduced on an individual basis, e.g. to a dose that results in minimal clotting in the bubble trap.

LMWHs

LMWHs are depolymerized fractions of heparin, and consequently consist of smaller units. LMWHs are effective inhibitors of factor Xa. Because their size is smaller than unfractionated heparin, LMWHs are not able to form a complex with AT-III. Therefore, their effect on thrombin is markedly less pronounced than that of unfractionated heparin. LMWHs not only are smaller but also less negatively charged. This results in reduced non-specific binding to plasma proteins and improved bioavailability.

A number of LMWHs are at present available. Several studies have revealed that the efficacy of LMWHs is at least as good as that of unfractionated heparin [32,33]. Initially dosing schedules included bolus injections followed by continuous infusion as with unfractionated heparin [34–39]. Subsequent studies have demonstrated that a single bolus injection is usually suffice to avoid clotting of the extracorporeal system [32,40–51]. In some papers it is advocated, however, to give additional LMWH (as a bolus or continuous infusion) when the length of the dialysis sessions exceeds 4 h [48,52]. At doses sufficient to prevent anticoagulation of the extracorporeal circuit, LMWHs may not prevent increases of activation markers of platelets and the coagulation system during haemodialysis [53].

For dose examples of the various LMWHs, the reader is referred to the prescriptions suggested by the manufacturer, commonly reported in the pocket insert.

Although no data are available at present, it can be advised for patients already using agents that affect clotting (i.e. anti-platelet agents or anti-vitamin K) to reduce the dose of LMWH on an individual base, e.g. to a dose that results in minimal clotting in the bubble trap. In one study, it was demonstrated that the dose of LMWH was not affected by the use of low- or high-permeable membranes [44].

Commentary on Guideline V.2.2

Several reasons can be given to advocate LMWHs as principal anticoagulant agents for routine haemodialysis compared with unfractionated heparin. First, the convenience of a single bolus injection, that has been demonstrated to have an equally effective anticoagulant effect as a continuous infusion of low-dose unfractionated heparin [32,40–51], make LMWH more easy to handle. In addition to this, Hofbauer *et al.* [33], utilizing scanning electron microscopy, recently demonstrated that membrane-associated clotting was less after treatment with LMWH compared with unfractionated heparin.

Secondly, unfractionated heparin has not only an anticoagulant effect but also stimulates plasma lipolytic activity [54,55], which results in hydrolysis of triglycerides and free fatty acids. It has been demonstrated that the effects on serum lipids are diminished when the heparin dosage is reduced [6]. In addition, a number of papers have reported on a beneficial effect of LMWH treatment on lipid profiles. This has been demonstrated after switching from unfractionated heparin to LMWH and especially so in selected patient groups (i.e. patients with elevated total cholesterol and/or triglycerides). LMWH treatment, for prospective follow-up periods ranging from 6 months to 4 years, significantly reduced total cholesterol [56–61] and triglyceride levels [56,59–61]. Likewise, a reduction in LDL [58,61] and VLDL [61] was observed during LMWH treatment whereas a modest fall [58,60] or rise [59] in HDL has been observed. Elisaf *et al.* [62,63] demonstrated in an unselected patient group of 76 patients that after 12 months of LMWH treatment total cholesterol, triglyceride, and Apo B had decreased. After this 1-year period, patients were randomly selected to either continue LMWH or switch back to unfractionated heparin for another year. In LMWH-treated patients, the lipid profile improved further, whereas in the unfractionated heparin-treated patients lipid profile did not change [63]. In contrast with the above-mentioned observations, Kronenberg *et al.* [64], however, did not find differences in serum total cholesterol, triglycerides, LDL, and Apo B between 153 LMWH-treated and 153 unfractionated heparin-treated haemodialysis patients. In addition, these investigators demonstrated that in patients who were switched from LMWH to unfractionated heparin after 6 months of haemodialysis treatment, serum total cholesterol, triglycerides, and LDL had declined

significantly [65]. In summary, it can be concluded that despite the latter two observations, in the majority of studies the use of LMWHs did improve serum lipid profiles. It has not been demonstrated, however, that in dialysis patients this improvement of lipid profiles towards a less atherogenic profile during LMWH-treatment leads to less cardiovascular disease. Nevertheless, given the high rate of cardiovascular disease in these patients, treatment strategies that possibly affect cardiovascular risk beneficially, such as LMWH instead of unfractionated heparin, seem to be justified.

Thirdly, in a few studies it was shown that patients treated with LMWHs needed fewer blood transfusions [39,66]. In addition, it is known from the treatment of patients with thrombo-embolism that LMWHs are at least as effective as unfractionated heparin with a trend towards a reduced bleeding risk [67,68].

Finally, a less well-known side effect of heparin therapy seen in patients treated with heparin, e.g. because of thrombo-embolism, is hyperkalaemia [69–79]. This is caused by heparin-induced inhibition of adrenal aldosterone production [70,80,81]. Especially patients with diabetes mellitus and chronic renal failure seem to be at risk [69,74,76,81,82]. It has been demonstrated that a dose-dependent suppression of mineralocorticoid metabolism occurs during treatment with unfractionated heparin and LMWH, albeit to a lesser degree in LMWH-treatment [80]. Compared with unfractionated heparin, LMWH-treatment resulted in a lower plasma potassium in haemodialysis patients [82,83]. If confirmed by other studies, this could be an additional argument to prefer LMWH over unfractionated heparin in haemodialysis patients.

Disadvantages of LMWHs over unfractionated heparin include the lack of assays that can easily measure anti-Xa activity [12,84] and the fact that their anticoagulant effect can be blocked only partially by protamine [85].

Commentary on Guideline V.3.1

No anticoagulants

In patients with increased risk for bleeding, such as the phase immediately before and after surgery or in case of gastrointestinal blood loss, haemodialysis without anticoagulation can be applied [86–98]. The risk for severe clotting in the extracorporeal system during this procedure has been reported to range from 0 to 20% [87,89,91–93,95]. Minor clotting usually did not affect the efficacy of the haemodialysis treatment. In most series the extracorporeal system was flushed with saline 0.9% (100–300 ml every 30 min) [90,91,93,96]. The important conditions for heparin-free dialysis are the removal of all air from the dialyzer during the priming operation, absolute prevention of air introduction in the extracorporeal circuit during dialysis and a high blood flow rate from the beginning of treatment. System clotting can also be prevented by prophylactically changing the dialyzer and blood lines [93].

Regional citrate anticoagulation

The administration of citrate to the arterial blood line will result in binding of ionized calcium which causes inhibition of the clotting cascade in the dialyzer and can thus be used for regional anticoagulation [98–100]. This technique requires the use of a calcium (and magnesium)-free dialysis fluid, and usually is performed by using trisodium citrate (for dosing details see [101]). Care must be taken not to sterilize trisodium citrate in glass bottles because this will result in accumulation of aluminium in the infusate. Citrate should, therefore, be sterilized in polypropylene bottles [101]. Because substitution of calcium and magnesium in the venous line (for dosing details see [101]) is mandatory to restore the clotting capacity of the blood, the technique of regional citrate anticoagulation requires two infusion pumps. Severe metabolic alkalosis has been described when citrate anticoagulation is performed in combination with bicarbonate dialysis fluid. Thus, the use of an adjusted dialysis fluid is necessary. Likewise, care has to be taken for appropriate substitution of calcium into the venous line as severe hypocalcaemia with potentially life-threatening cardiac arrhythmias may ensue. Altogether, the complexity of the technique of regional citrate anticoagulation does not make the technique suitable for routine dialysis. Nevertheless, use of regional citrate anticoagulation is especially suitable for patients with active bleeding or a high risk for bleeding [101–105].

Miscellaneous

Several reports have demonstrated that prostacyclin infusion (0.4–0.5 ng/kg/min) can be used safely in patients with a high bleeding risk to prevent clotting in the extracorporeal system [106–108]. Side effects such as flushing and intradialytic hypotension may occur

V.3 Prevention of clotting in the HD patient with elevated bleeding risk

Guideline V.3.1

A. In patients with increased bleeding risks, strategies that can induce systemic anticoagulation should be avoided. Treatments strategies that avoid this include: no use of anticoagulants with regular saline flushing or regional citrate anticoagulation.

(Evidence level: A)

Guideline V.3.2

A. Regional heparinization should not be performed because of increased risk of bleeding after dialysis.

(Evidence level: A)

[106,107]. Usually these side effects do not prevent continuation of treatment with prostacyclin, making cost the only disadvantage of prostacyclin.

Commentary on Guideline V.3.2

Regional heparinization (i.e. heparin administration into the arterial line and protamine into the venous line) has no advantages over low-dose heparin alone. It has been demonstrated that after such regional heparinization a rebound anti-coagulant effect can be observed due to the shorter half-life of protamine compared with that of heparin [109,110]. In fact, the bleeding complications with regional heparinization appear to be more frequent than with low-dose heparin [110]. Thus, the use of regional heparinization is not recommended.

haemodialysed employing low-molecular weight heparanoid (danaparoid) [123–126] or direct thrombin inhibitors (recombinant hirudin [127–129] or argatroban [130]). For dosing of these agents, the reader is referred to the prescriptions suggested by the manufacturer, as reported in the pocket insert. When patients with type II HIT are re-exposed to heparin, thrombocytopenia will develop frequently [131]. Of course, transfer to CAPD or CCPD can be considered in patients with type II HIT.

Danaparoid consists of a mixture of dermatan sulfate and low-sulfated heparan sulfate. It has anti-factor Xa activity but hardly an effect on thrombin or platelets. Danaparoid has been used successfully in haemodialysis patients with type II HIT [132–134]. Its major disadvantages are the need to determine anti-Xa concentrations to monitor its anticoagulant efficacy, its long half-life (25 ± 100 h) in renal failure, the absence of a useful reversing agent, and its high cost.

Recombinant hirudin is another agent that can be used for routine haemodialysis in patients with type II HIT [127–129]. Hirudin is a specific inhibitor of thrombin on a 1:1 ratio. It has been used with success in patients with type II HIT. Similarly to danaparoid, disadvantages of hirudin are the lack of a reliable biochemical test system for monitoring its anticoagulant effect, and the pronounced and variably prolonged half-life in dialysis patients and especially in anuric patients [135].

V.4 Heparin-induced thrombocytopenia

Guideline V.4

A. In heparin-induced thrombocytopenia (HIT), prevention of clotting should be with heparanoids, hirudin, or citrate anticoagulation.

(Evidence level: A)

Commentary on Guideline V.4

Type I HIT can be observed in patients treated with heparin [111–113]. It is characterized by a reduction in platelet count occurring within 5 days after initiation of heparin. It is transient on continuation of heparin and has no clinical consequences.

In contrast, type II HIT is a more severe complication of heparin treatment that is antibody-mediated [112,113]. The antibodies are directed against the complex of heparin and platelet factor 4 [114–116]. Platelet counts can decline severely but usually remain $> 20\,000/\mu\text{l}$. Consequently, severe bleeding complications are rare. The prevalence of type II HIT is rare (1–3% in heparin-treated patients [113]) but has been described in haemodialysis patients [117–120]. Its main clinical complication is the development of thrombosis, including arterial thrombosis. Thrombosis has been observed in up to 60% of heparin-treated patients with serologically confirmed HIT. The initial step in the diagnosis of HIT is to be aware of it as a cause of thrombocytopenia in heparin-treated patients. Specific tests for demonstrating type II HIT are the serotonin release assays, heparin-induced platelet aggregation assays, and solid-phase immunoassays [121,122].

Treatment of type II HIT starts with the total avoidance of heparin. In addition, the use of LMWHs should be discouraged because cross-reaction with heparin-induced antibodies and heparin-dependent IgG antibody formation has been described. Patients with confirmed type II HIT can be routinely

V.5 Side effects of heparin

Guideline V.5

A. When side effects of heparin therapy during routine haemodialysis occur, the use of unfractionated heparin has to be avoided.

(Evidence level: B)

Commentary on Guideline V.5

Miscellaneous side effects of treatment with unfractionated heparin have been described [136], including severe skin necrosis, hypersensitivity, osteoporosis, and hyperkalaemia. In those patients the use of heparin should be avoided.

Hypersensitivity

A few case reports of a generalized cutaneous hypersensitivity reaction to porcine heparin preparations have been described. Immunological studies in these patients reveal IgE and IgG antibodies directed to heparin or to contaminants of the preparation [137,138].

Severe skin necrosis

In patients treated with continuous administration of heparin, severe skin necrosis is a rare but

well-documented complication. Likewise, this complication has been described in a few patients on chronic haemodialysis therapy without development of thrombocytopenia [139,140]. Skin necrosis appears to be a very severe complication of heparin treatment with poor outcome, despite discontinuation of heparin.

References

- Panichi V, Casarosa L, Gattai V *et al.* Protein layer on hemodialysis membranes: a new immunohistochemistry technique. *Int J Artif Organs* 1995; 18: 305–308 (B)
- Cases A, Reverter JC, Escolar G *et al.* *In vivo* evaluation of platelet activation by different cellulosic membranes. *Artif Organs* 1997; 21: 330–334 (B)
- Kolb G, Fischer W, Seitz R *et al.* Hemodialysis and blood coagulation: the effect of hemodialysis on coagulation factor XIII and thrombin-antithrombin III complex. *Nephron* 1991; 58: 106–108 (B)
- Ishii Y, Yano S, Kanai H *et al.* Evaluation of blood coagulation-fibrinolysis system in patients receiving chronic hemodialysis. *Nephron* 1996; 73: 407–412 (B)
- Seyfert UT, Helmling E, Hauck W, Skroch D, Albert W. Comparison of blood biocompatibility during haemodialysis with cuprophane and polyacrylonitrile membranes. *Nephrol Dial Transplant* 1991; 6: 428–434 (B)
- Sperschneider H, Deppisch R, Beck W, Wolf H, Stein G. Impact of membrane choice and blood flow pattern on coagulation and heparin requirement—potential consequences on lipid concentrations. *Nephrol Dial Transplant* 1997; 12: 2638–2646 (A)
- Wright MJ, Woodrow G, Umpleby S *et al.* Low thrombogenicity of polyethylene glycol-grafted cellulose membranes does not influence heparin requirements in hemodialysis. *Am J Kidney Dis* 1999; 34: 36–42 (A)
- Sultan Y, London GM, Goldfarb B, Toulon P, Marchais SJ. Activation of platelets, coagulation and fibrinolysis in patients on long-term haemodialysis: influence of cuprophane and polyacrylonitrile membranes. *Nephrol Dial Transplant* 1990; 5: 362–368 (B)
- Moll S, De Moerloose P, Reber G, Schifferli J, Leski M. Comparison of two hemodialysis membranes, polyacrylonitrile and cellulose acetate, on complement and coagulation systems. *Int J Artif Organs* 1990; 13: 273–279 (B)
- Reber G, Stoermann C, De Moerloose P, Ruedin P, Leski M. Hemostatic disturbances induced by two hollow-fiber hemodialysis membranes. *Int J Artif Organs* 1992; 15: 269–276 (B)
- Mujais SK, Schmidt B, Hacker H, Opatrny K, Gurland HJ. Synthetic modification of PAN membrane: biocompatibility and functional characterization. *Nephrol Dial Transplant* 1995; 10 [Suppl 3]: 46–51 (A)
- Greiber S, Weber U, Galle J, Bramer P, Schollmeyer P. Activated clotting time is not a sensitive parameter to monitor anticoagulation with low molecular weight heparin in hemodialysis. *Nephron* 1997; 76: 15–19 (B)
- Leitienne P, Trzeciak MC, Adeleine P *et al.* Comparison of hemostasis with two high-flux hemocompatible dialysis membranes. *Int J Artif Organs* 1991; 14: 227–233 (A)
- Verbeelen D, Jochmans K, Herman AG *et al.* Evaluation of platelets and hemostasis during hemodialysis with six different membranes. *Nephron* 1991; 59: 567–572 (A)
- Mingardi G, Perico N, Pusineri F *et al.* Heparin for hemodialysis: practical guidelines for administration and monitoring. *Int J Artif Organs* 1984; 7: 269–274 (B)
- Ireland H, Lane DA, Curtis JR. Objective assessment of heparin requirements for hemodialysis in humans. *J Lab Clin Med* 1984; 103: 643–652 (B)
- Low CL, Bailie G, Morgan S, Eisele G. Effect of a sliding scale protocol for heparin on the ability to maintain whole blood activated partial thromboplastin times within a desired range in hemodialysis patients. *Clin Nephrol* 1996; 45: 120–124 (A)
- Seifert R, Borchert W, Letendre P, Knutson R, Cipolle R. Heparin kinetics during hemodialysis: variation in sensitivity, distribution volume, and dosage. *Ther Drug Monit* 1986; 8: 32–36 (B)
- Ward RA. Heparinization for routine hemodialysis. *Adv Ren Replace Ther* 1995; 2: 362–370 (B)
- Ouseph R, Ward RA. Anticoagulation for intermittent hemodialysis. *Semin Dial* 2000; 13: 181–187 (B)
- Mitsuoka JC. A calculator program to determine heparin requirements during hemodialysis. *Comput Biol Med* 1983; 13: 239–243 (C)
- Farrell PC, Ward RA, Schindhelm K, Gotch F. Precise anticoagulation for routine hemodialysis. *J Lab Clin Med* 1978; 92: 164–176 (B)
- Smith BP, Ward RA, Brier ME. Prediction of anticoagulation during hemodialysis by population kinetics and an artificial neural network. *Artif Organs* 1998; 22: 731–739 (B)
- Opatrny K Jr, Bouda M, Kohoutkova L, Vit L, Sefrna F. A clinical study to assess the effect of heparin in dialyzer rinsing solutions. *Int J Artif Organs* 1997; 20: 112–118 (A)
- Buturovic J, Zemva Z, Ponikvar R. Filling a dialysis circuit with albumin does not prevent platelet activation during hemodialysis: *in vivo* study. *Artif Organs* 1994; 18: 875–879 (B)
- Spinowitz BS, Arslanian J, Charytan C *et al.* Impact of epoetin beta on dialyzer clearance and heparin requirements. *Am J Kidney Dis* 1991; 18: 668–673 (B)
- Norton J, Spiezio R, LaManna L, DeLorme B. Varying heparin requirements in hemodialysis patients receiving erythropoietin. *ANNA J* 1940; 19: 367–372 (B)
- Taylor JE, Belch JJ, McLaren M, Henderson IS, Stewart WK. Effect of erythropoietin therapy and withdrawal on blood coagulation and fibrinolysis in hemodialysis patients. *Kidney Int* 1993; 44: 182–190 (B)
- Veys N, Vanholder R, De Cuyper K, Ringoir S. Influence of erythropoietin on dialyzer reuse, heparin need, and urea kinetics in maintenance hemodialysis patients. *Am J Kidney Dis* 1994; 23: 52–59 (B)
- Clyne N, Lins LE, Egberg N. Long-term effects of erythropoietin treatment on the coagulation system during standardized hemodialysis. *Clin Nephrol* 1995; 43: 260–267 (B)
- Ward RA, Schmidt B, Gurland HJ. Prevention of blood loss in dialysers with DEAE-cellulose membranes does not require increased doses of heparin. *Nephrol Dial Transplant* 1993; 8: 1140–1145 (A)
- Moia M, Graziani G, Tenconi PM, Martinelli I, Ponticelli C. Rationale for the use of a low molecular weight heparin during hemodialysis with polysulphone membrane in uremic patients. *Annali Ital Med Interna* 1997; 12: 67–71 (A)
- Hofbauer R, Moser D, Frass M *et al.* Effect of anticoagulation on blood membrane interactions during hemodialysis. *Kidney Int* 1999; 56: 1578–1583 (B)
- Lane DA, Flynn A, Ireland H, Anastassiades E, Curtis JR. On the evaluation of heparin and low molecular weight heparin in haemodialysis for chronic renal failure. *Haemostasis* 1986; 16 [Suppl 2]: 38–47 (B)
- Borm JJ, Krediet R, Sturk A, ten Cate J. Heparin versus low molecular weight heparin K 2165 in chronic hemodialysis patients: a randomized cross-over study. *Haemostasis* 1986; 16 [Suppl 2]: 59–68 (A)
- Anastassiades E, Lane DA, Ireland H, Flynn A, Curtis JR. A low molecular weight heparin ('fragmin') for routine hemodialysis: a crossover trial comparing three dose regimens with a standard regimen of commercial unfractionated heparin. *Clin Nephrol* 1989; 32: 290–296 (A)
- Ryan KE, Lane DA, Flynn A *et al.* Dose finding study of a low molecular weight heparin, Innohep, in haemodialysis. *Thromb Haemost* 1991; 66: 277–282 (B)
- Hafner G, Klingel R, Wandel E *et al.* Laboratory control of minimal heparinization during haemodialysis in patients with a risk of haemorrhage. *Blood Coagul Fibrinolysis* 1994; 5: 221–226 (B)
- Schrader J, Stubbe W, Armstrong VW *et al.* Comparison of low molecular weight heparin to standard heparin in hemodialysis/hemofiltration. *Kidney Int* 1988; 33: 890–896 (A)

40. Ljungberg B, Blomback M, Johnsson H, Lins LE. A single dose of a low molecular weight heparin fragment for anticoagulation during hemodialysis. *Clin Nephrol* 1987; 27: 31–35 (B)
41. Nurmohamed MT, ten Cate J, Stevens P *et al.* Long-term efficacy and safety of a low molecular weight heparin in chronic hemodialysis patients. A comparison with standard heparin. *ASAIO Trans* 1991; 37: M459–M461 (A)
42. Ljungberg B, Jacobson SH, Lins LE, Pejler G. Effective anticoagulation by a low molecular weight heparin (Fragmin) in hemodialysis with a highly permeable polysulfone membrane. *Clin Nephrol* 1992; 38: 97–100 (B)
43. Grau E, Siguenza F, Maduell F *et al.* Low molecular weight heparin (CY-216) versus unfractionated heparin in chronic hemodialysis. *Nephron* 1992; 62: 13–17 (B)
44. Baumelou A, Singlas E, Petitclerc T *et al.* Pharmacokinetics of a low molecular weight heparin (reviparine) in hemodialyzed patients. *Nephron* 1994; 68: 202–206 (B)
45. Koutsikos D, Fourtounas C, Kapetanaki A *et al.* A cross-over study of a new low molecular weight heparin (Logiparin) in hemodialysis. *Int J Artif Organs* 1996; 19: 467–471 (B)
46. Simpson HK, Baird J, Allison M *et al.* Long-term use of the low molecular weight heparin tinzaparin in haemodialysis. *Haemostasis* 1996; 26: 90–97 (B)
47. Lai KN, Wang AY, Ho K *et al.* Use of low-dose low molecular weight heparin in hemodialysis. *Am J Kidney Dis* 1996; 28: 721–726 (B)
48. Lai KN, Ho K, Li M, Szeto CC. Use of single dose low-molecular-weight heparin in long hemodialysis. *Int J Artif Organs* 1998; 21: 196–200 (B)
49. Egfjord M, Rosenlund L, Hedegaard B *et al.* Dose titration study of tinzaparin, a low molecular weight heparin, in patients on chronic hemodialysis. *Artif Organs* 1998; 22: 633–637 (B)
50. Saltissi D, Morgan C, Westhuyzen J, Healy H. Comparison of low-molecular-weight heparin (enoxaparin sodium) and standard unfractionated heparin for haemodialysis anticoagulation. *Nephrol Dial Transplant* 1999; 14: 2698–2703 (A)
51. Sagedal S, Hartmann A, Sundstrom K *et al.* A single dose of dalteparin effectively prevents clotting during haemodialysis. *Nephrol Dial Transplant* 1999; 14: 1943–1947 (B)
52. Van Hoof A, Schurgers M, Boelaert J, Criel A. Low-molecular-weight heparin dosage in haemodialysis. *Nephrol Dial Transplant* 1987; 2: 193–194 (B)
53. Sagedal S, Hartmann A, Sundstrøm K, Bjørnsen S, Brosstad F. Anticoagulation intensity sufficient for haemodialysis does not prevent activation of coagulation and platelets. *Nephrol Dial Transplant* 2001; 16: 987–993 (B)
54. Schrader J, Andersson LO, Armstrong VW *et al.* Lipolytic effects of heparin and low molecular weight heparin and their importance in hemodialysis. *Semin Thromb Hemost* 1990; 16 [Suppl]: 41–45 (B)
55. Arnadottir M, Kurkus J, Nilsson-Ehle P. Different types of heparin in haemodialysis: long-term effects on post-heparin lipases. *Scand J Clin Lab Invest* 1994; 54: 515–521 (B)
56. Deuber HJ, Schulz W. Reduced lipid concentrations during four years of dialysis with low molecular weight heparin. *Kidney Int* 1991; 40: 496–500 (B)
57. Akiba T, Tachibana K, Ozawa K *et al.* Long-term use of low molecular weight heparin ameliorates hyperlipidemia in patients on hemodialysis. *ASAIO J* 1992; 38: M326–M330 (B)
58. Schmitt Y, Schneider H. Low-molecular-weight heparin (LMWH): influence on blood lipids in patients on chronic haemodialysis. *Nephrol Dial Transplant* 1993; 8: 438–442 (B)
59. Vlassopoulos D, Noussias C, Hadjipetrou A *et al.* Long-term effect of low molecular weight heparin on serum lipids in hypertriglyceridemic chronic hemodialysis patients. *J Nephrol* 1997; 10: 111–114 (B)
60. Yang C, Wu T, Huang C. Low molecular weight heparin reduces triglyceride, VLDL and cholesterol/HDL levels in hyperlipidemic diabetic patients on hemodialysis. *Am J Nephrol* 1998; 18: 384–390 (B)
61. Leu JG, Liou HH, Wu SC, Yang WC, Huang TP. Low molecular weight heparin in diabetic and nondiabetic hypercholesterolemic patients receiving long-term hemodialysis. *J Form Med Assoc* 1998; 97: 49–54 (B)
62. Elisaf MS, Bairaktari H, Germanos N *et al.* Long-term effects of low molecular weight heparin on lipid parameters in hemodialysis patients. *Int Angiol* 1996; 15: 252–256 (B)
63. Elisaf MS, Germanos NP, Bairaktari HT *et al.* Effects of conventional vs. low-molecular-weight heparin on lipid profile in hemodialysis patients. *Am J Nephrol* 1997; 17: 153–157 (A)
64. Kronenberg F, König P, Neyer U *et al.* Influence of various heparin preparations on lipoproteins in hemodialysis patients: a multicentre study. *Thromb Haemost* 1995; 74: 1025–1028 (B)
65. Kronenberg F, König P, Lhotta K, Steinmetz A, Dieplinger H. Low molecular weight heparin does not necessarily reduce lipids and lipoproteins in hemodialysis patients. *Clin Nephrol* 1995; 43: 399–404 (B)
66. Bambaue R, Rucker S, Weber U, Kohler M. Comparison of low molecular weight heparin and standard heparin in hemodialysis. *ASAIO Trans* 1990; 36: M646–M649 (B)
67. Bijsterveld NR, Hettiarachchi R, Peters R *et al.* Low-molecular weight heparins in venous and arterial thrombotic disease. *Thromb Haemost* 1999; 82 [Suppl 1]: 139–147 (B)
68. Dolovich LR, Ginsberg JS, Douketis JD, Holbrook AM, Cheah G. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. *Arch Intern Med* 2000; 160: 181–188 (A)
69. Phelps KR, Oh MS, Carroll HJ. Heparin-induced hyperkalemia: report of a case. *Nephron* 1980; 25: 254–258 (B)
70. Leehey D, Gantt C, Lim V. Heparin-induced hypoaldosteronism. Report of a case. *J Am Med Assoc* 1981; 246: 2189–2190 (B)
71. Edes TE. Heparin-induced hyperkalemia. *Postgrad Med* 1990; 87: 104–106 (B)
72. Quintanilla AP, Weffer MI. Hyperkalemia in the patient on chronic dialysis. *Int J Artif Organs* 1987; 10: 17–19 (B)
73. Maddux FW. Heparin-induced hyperkalemia. *N C Med J* 1987; 48: 75–76 (B)
74. Busch EH, Ventura HO, Lavie CJ. Heparin-induced hyperkalemia. *South Med J* 1987; 80: 1450–1451 (B)
75. Monreal M, Lafoz E, Salvador R, Roncales J, Navarro A. Adverse effects of three different forms of heparin therapy: thrombocytopenia, increased transaminases, and hyperkalemia. *Eur J Clin Pharmacol* 1989; 37: 415–418 (B)
76. Aull L, Chao H, Coy K. Heparin-induced hyperkalemia. *DICP: Ann Pharmacotherap* 1990; 24: 244–246 (B)
77. Gonzalez-Martin G, Diaz-Molinias MS, Martinez AM, Ortiz M. Heparin-induced hyperkalemia: a prospective study. *Int J Clin Pharmacol Ther Toxicol* 1991; 29: 446–450 (B)
78. Bacon NC. Heparin-induced disturbance of potassium homeostasis. *Q J Med* 1997; 90: 725 (B)
79. Orlando MP, Dillon ME, O'Dell MW. Heparin-induced hyperkalemia confirmed by drug rechallenge. *Am J Phys Med Rehabil* 2000; 79: 93–96 (B)
80. Siebels M, Andrassy K, Vecsei P *et al.* Dose dependent suppression of mineralocorticoid metabolism by different heparin fractions. *Thromb Res* 1992; 66: 467–473 (B)
81. Oster JR, Singer I, Fishman LM. Heparin-induced aldosterone suppression and hyperkalemia. *Am J Med* 1995; 98: 575–586 (B)
82. Edes TE, Sunderrajan EV. Heparin-induced hyperkalemia. *Arch Intern Med* 1985; 145: 1070–1072 (B)
83. Hottelart C, Achard JM, Moriniere P *et al.* Heparin-induced hyperkalemia in chronic hemodialysis patients: comparison of low molecular weight and unfractionated heparin. *Artif Organs* 1998; 22: 614–617 (A)
84. Messmore HL. Clinical efficacy of heparin fractions: issues and answers. *Crit Rev Clin Lab Sci* 1986; 23: 77–94 (B)
85. Andrassy K. Low molecular weight heparin and haemodialysis: neutralization by protaminchloride. *Blood Coagul Fibrinolysis* 1993; 4 [Suppl 1]: S39–S43 (B)
86. Glaser P, Guesde R, Roubey JJ, Eurin B. Haemodialysis without heparin is possible. *Lancet* 1979; 2: 579–580 (B)
87. Casati S, Graziani G, Ponticelli C. Hemodialysis without anticoagulants in patients with high bleeding risk. *Int J Artif Organs* 1982; 5: 233–236 (B)
88. Hathiwal S. Dialysis without anticoagulation. *Int J Artif Organs* 1983; 6: 64–66 (B)

89. Casati S, Moia M, Graziani G *et al.* Hemodialysis without anticoagulants: efficiency and hemostatic aspects. *Clin Nephrol* 1984; 21: 102–105 (B)
90. Agresti J, Conroy JD, Olshan A *et al.* Heparin-free hemodialysis with Cuprophan hollow fiber dialyzers by a frequent saline flush, high blood flow technique. *ASAIO Trans* 1985; 31: 590–594 (B)
91. Sanders PW, Taylor H, Curtis JJ. Hemodialysis without anticoagulation. *Am J Kidney Dis* 1985; 5: 32–35 (B)
92. Caruana RJ, Raja RM, Bush JV, Kramer MS, Goldstein SJ. Heparin free dialysis: comparative data and results in high risk patients. *Kidney Int* 1987; 31: 1351–1355 (B)
93. Preuschhof L, Keller F, Seemann J, Offermann G. Heparin-free hemodialysis with prophylactic change of dialyser and blood lines. *Int J Artif Organs* 1988; 11: 255–258 (B)
94. Ludlow MK. Heparin-free dialysis. *ANNA J* 1989; 16: 295–298 (B)
95. Keller F, Seemann J, Preuschhof L, Offermann G. Risk factors of system clotting in heparin-free haemodialysis. *Nephrol Dial Transplant* 1990; 5: 802–807 (B)
96. Geary DF, Gajaria M, Fryer-Keene S, Willumsen J. Low-dose and heparin-free hemodialysis in children. *Ped Nephrol* 1991; 5: 220–224 (B)
97. Mujais SK, Chimeh H. Heparin free hemodialysis using heparin coated hemophan. *ASAIO J* 1996; 42: M538–M541 (A)
98. von Brecht J, Flanigan MJ, Freeman RM, Lim VS. Regional anticoagulation: hemodialysis with hypertonic trisodium citrate. *Am J Kidney Dis* 1986; 8: 196–201 (B)
99. Wiegmann TB, MacDougall ML, Diederich DA. Long-term comparisons of citrate and heparin as anticoagulants for hemodialysis. *Am J Kidney Dis* 1987; 9: 430–435 (A)
100. Van der Meulen J, Janssen MJ, Langendijk PN, Bouman AA, Oe PL. Citrate anticoagulation and dialysate with reduced buffer content in chronic hemodialysis. *Clin Nephrol* 1992; 37: 36–41 (B)
101. Janssen MJ, Deegens JK, Kapinga TH *et al.* Citrate compared to low molecular weight heparin anticoagulation in chronic hemodialysis patients. *Kidney Int* 1996; 49: 806–813 (A)
102. Pinnick RV, Wiegmann TB, Diederich DA. Regional citrate anticoagulation for hemodialysis in the patient at high risk for bleeding. *N Eng J Med* 1983; 308: 258–261 (B)
103. Flanigan MJ, Von BJ, Freeman RM, Lim VS. Reducing the hemorrhagic complications of hemodialysis: a controlled comparison of low-dose heparin and citrate anticoagulation. *Am J Kidney Dis* 1987; 9: 147–153 (A)
104. Janssen MJ, Huijgens PC, Bouman AA *et al.* Citrate versus heparin anticoagulation in chronic haemodialysis patients. *Nephrol Dial Transplant* 1993; 8: 1228–1233 (B)
105. Janssen MJ, van der Meulen J. The bleeding risk in chronic haemodialysis: preventive strategies in high-risk patients. *Neth J Med* 1996; 48: 198–207 (B)
106. Smith MC, Danviriyasup K, Crow JW *et al.* Prostacyclin substitution for heparin in long-term hemodialysis. *Am J Med* 1982; 73: 669–678 (B)
107. Caruana RJ, Smith MC, Clyne D, Crow JW, Zinn JM, Hall Diehl J. Controlled study of heparin versus epoprostenol sodium (prostacyclin) as the sole anticoagulant for chronic hemodialysis. *Blood Purif* 1991; 9: 296–304 (B)
108. Swartz RD, Flamenbaum W, Dubrow A, Hall JC, Crow JW, Cato A. Epoprostenol (PGI₂, prostacyclin) during high-risk hemodialysis: preventing further bleeding complications. *J Clin Pharmacol* 1988; 28: 818–825 (B)
109. Blaufox MD, Hampers CL, Merrill JP. Rebound anticoagulation occurring after regional heparinization for hemodialysis. *ASAIO Trans* 1966; 12: 207–209 (B)
110. Swartz RD, Port FK. Preventing hemorrhage in high-risk hemodialysis: regional versus low-dose heparin. *Kidney Int* 1979; 16: 513–518 (A)
111. Chong B, Castaldi P. Platelet proaggregating effect of heparin: possible mechanism for non-immune heparin-associated thrombocytopenia. *Aust N Z J Med* 1986; 16: 715–716 (B)
112. Greinacher A. Antigen generation in heparin-associated thrombocytopenia: the nonimmunologic type and the immunologic type are closely linked in their pathogenesis. *Semin Thromb Hemost* 1995; 21: 106–116 (B)
113. Warkentin TE, Chong BH, Greinacher A. Heparin-induced thrombocytopenia: towards consensus. *Thromb Haemost* 1998; 79: 1–7 (B)
114. Amiral J, Bridey F, Dreyfus M *et al.* Platelet factor 4 complexed to heparin is the target for antibodies generated in heparin-induced thrombocytopenia. *Thromb Haemost* 1992; 68: 95–96 (B)
115. Visentin GP, Ford SE, Scott JP, Aster RH. Antibodies from patients with heparin-induced thrombocytopenia/thrombosis are specific for platelet factor 4 complexed with heparin or bound to endothelial cells. *J Clin Invest* 1994; 93: 81–88 (B)
116. Sitter T, Spannagl M, Banas B, Schiffel H. Prevalence of heparin-induced PF4-heparin antibodies in hemodialysis patients. *Nephron* 1998; 79: 245–246 (B)
117. Leehey DJ, Kanak RJ, Messmore HL *et al.* Heparin-associated thrombocytopenia in maintenance hemodialysis patients. *Int J Artif Organs* 1987; 10: 390–392 (B)
118. Hall AV, Clark WF, Parbtani A. Heparin-induced thrombocytopenia in renal failure. *Clin Nephrol* 1992; 38: 86–89 (B)
119. Finazzi G, Remuzzi G. Heparin-induced thrombocytopenia—background and implications for haemodialysis. *Nephrol Dial Transplant* 1996; 11: 2120–2122 (B)
120. Yamamoto S, Koide M, Matsuo M *et al.* Heparin-induced thrombocytopenia in hemodialysis patients. *Am J Kidney Dis* 1996; 28: 82–85 (B)
121. Kelton JG. The serological investigation of patients with autoimmune thrombocytopenia. *Thromb Haemost* 1995; 74: 228–233 (B)
122. Kelton JG, Warkentin TE. Diagnosis of heparin-induced thrombocytopenia. Still a journey, not yet a destination. *Am J Clin Pathol* 1995; 104: 611–613 (B)
123. Henny CP, ten Cate H, Surachno S *et al.* The effectiveness of a low molecular weight heparinoid in chronic intermittent haemodialysis. *Thromb Haemost* 1985; 54: 460–462 (A)
124. Ireland H, Lane DA, Flynn A, Anastassiades E, Curtis JR. The anticoagulant effect of heparinoid Org 10172 during haemodialysis: an objective assessment. *Thromb Haemost* 1986; 55: 271–275 (B)
125. Von Bonsdorf M, Stiekema J, Harjanne A, Alapiessa U. A new low molecular weight heparinoid Org 10172 as anticoagulant in hemodialysis. *Int J Artif Organs* 1990; 13: 103–108 (A)
126. Striker GE. Therapeutic uses of heparinoids in renal disease patients. *Nephrol Dial Transplant* 1999; 14: 540–543 (B)
127. Vanholder RC, Camez AA, Veys NM *et al.* Recombinant hirudin: a specific thrombin inhibiting anticoagulant for hemodialysis. *Kidney Int* 1994; 45: 1754–1759 (A)
128. van Wijk V, Badenhorst PN, Luus HG, Kotze HF. A comparison between the use of recombinant hirudin and heparin during hemodialysis. *Kidney Int* 1995; 48: 1338–1343 (B)
129. Nowak G, Bucha E, Brauns I, Czerwinski R. Anticoagulation with r-hirudin in regular haemodialysis with heparin-induced thrombocytopenia (HIT II). The first long-term application of r-hirudin in a haemodialysis patient. *Wien Klin Wochenschr* 1997; 109: 354–358 (B)
130. Matsuo T, Kario K, Kodama K, Okamoto S. Clinical application of the synthetic thrombin inhibitor, argatroban (MD-805). *Semin Thromb Hemost* 1992; 18: 155–160 (B)
131. Laster J, Elfrink R, Silver D. Reexposure to heparin of patients with heparin-associated antibodies. *J Vasc Surg* 1989; 9: 677–681 (B)
132. Greinacher A, Philippen KH, Kemkes-Matthes B *et al.* Heparin-associated thrombocytopenia type II in a patient with end-stage renal disease: successful anticoagulation with the low-molecular-weight heparinoid Org 10172 during haemodialysis. *Nephrol Dial Transplant* 1993; 8: 1176–1177 (B)
133. Rowlings PA, Mansberg R, Rozenberg MC, Evans S, Murray B. The use of a low molecular weight heparinoid (Org 10172) for extracorporeal procedures in patients with

- heparin dependent thrombocytopenia and thrombosis. *Aust N Z J Med* 1991; 21: 52–54 (B)
134. Abuelo JG, Chang BS. Is prostacyclin better than nothing for anticoagulation in haemodialysis? *Lancet* 1981; 2: 470–471 (B)
135. Vanholder R, Camez A, Veys N, Van Loo A, Dhondt AM, Ringoir S. Pharmacokinetics of recombinant hirudin in hemodialyzed end-stage renal failure patients. *Thromb Haemost* 1997; 77: 650–655 (B)
136. Bick RL, Frenkel EP. Clinical aspects of heparin-induced thrombocytopenia and thrombosis and other side effects of heparin therapy. *Clin Appl Thromb Hemost* 1999; 5 [Suppl 1]: S7–S15 (B)
137. Rosenzweig P, Gary NE, Gocke DJ *et al.* Heparin allergy accompanying acute renal failure. *Artif Organs* 1979; 3: 78–79 (B)
138. Katoh S, Terashima S, Nakahara Y *et al.* Hypersensitivity to heparin, a case report. *Nippon Jinzo Gakkai Shi Jap J Nephrol* 1993; 35: 411–414 (B)
139. Leblanc M, Roy LF, Legault L *et al.* Severe skin necrosis associated with heparin in hemodialysis. *Nephron* 1994; 68: 133–137 (B)
140. Carrozza P, Gabutti L, Gilliet F, Marone C. Heparin-induced systemic inflammatory response syndrome with progressive skin necrosis in haemodialysis. *Nephrol Dial Transplant* 1997; 12: 2424–2427 (B)