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 extracorporal 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, Xa, 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]. Individual dosing schedules can reduce bleeding complications [21–23], but this usually requires mathematical 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

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Fig. 1. Overview of the coagulation cascade (PL = phospholipid).
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 sufficient to avoid clotting of the extracorporal 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 extracorporal 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 cloting 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 have 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].