

Commentary on Guideline VII.1

There is strong evidence from studies in the general population that cigarette smoking, glucose intolerance or diabetes control, hypertension, family history of vascular disease, and current or past history of vascular disease may each independently contribute to the risk of vascular disease [7–9]. Inclusion of a medical record history of vascular disease as a mortality case-mix factor is recommended in dialysis populations to quantify the presence of vascular disease and to estimate complications and outcome [10]. For dyslipidaemia and hypertension see separate guidelines (VII.2 and upcoming).

Glycaemic control

Glycaemic control before the start of dialysis has a major impact on patient survival. Amongst 137 patients with type 2 diabetes mellitus starting haemodialysis in a single centre, patients with good glycaemic control, 6 months before the start of treatment, had significantly greater 1- and 5-year survival than patients with poor control (1 year, 95.5 vs 80%; 5 year 75.8 vs 21.8%) [11].

Smoking

Smoking has been implicated as a cardiovascular risk factor in two early reports involving small numbers of patients [12]. Recent data show that smoking has an adverse effect on carotid atherosclerosis [13] and survival in diabetic patients on dialysis. Five-year survival in 22 smokers was 9% as compared with 30% in 30 non-smokers. Smokers also had an increased incidence of myocardial infarction (77 vs 13%), greater fibrinogen concentrations, and greater systolic blood pressure than non-smokers [14]. Recent cross-sectional studies in non-diabetic patients suggest that smokers on dialysis have carotid atherosclerosis more frequently than non-smokers [13,15,16]. This related to higher blood pressures and lower serum albumin concentrations [13].

VII.1 Assessment of cardiovascular risk factors

All patients on haemodialysis should be considered to be at the greatest risk of developing vascular disease. Measures to prevent vascular disease should not be based on the presence or absence of prior vascular disease or other risk factors, but should rather assume that the risk for vascular disease is already sufficient enough to warrant the most aggressive management.

Guideline VII.1

A. Patients' cardiovascular risk should be formally assessed and documented at the onset of haemodialysis and 6 months thereafter. Risk assessment includes modifiable risk factors such as cigarette smoking, hyperglycaemia, dyslipidaemia, and hypertension. (Evidence level: B)

VII.2 Dyslipidaemia

Guidelines on detection, evaluation, and treatment of high blood cholesterol in adults are available from

European and US expert panels [7] as well as from many national societies [8]. These guidelines are evidence-based and were developed for the general population in a rigorous manner. It is possible that trial results from the general population may not be applicable to patients on haemodialysis. There are no randomized controlled intervention trials in haemodialysis patients and even not in patients with chronic kidney disease showing that the treatment of dyslipidaemias reduces the incidence of vascular disease. It is possible that in some subpopulations of haemodialysis, treatment of dyslipidaemias may not be as safe, or as effective, in reducing the incidence of vascular disease, as it is in the general population. Therefore, the Work Group concluded that additional, randomized, placebo-controlled trials are urgently needed in patients on haemodialysis, and that the use of a placebo is justified in the context of an appropriately designed trial, even when lipid levels fall within the treatment thresholds recommended by these guidelines.

It was beyond the scope of this Work Group to repeat the process that produced the guidelines for the general population. A major focus, however, was to ascertain the extent to which the associations between the specific dyslipidaemias, addressed in the European and US guidelines, and atherosclerotic cardiovascular disease are similar in haemodialysis patients. Special attention was given to the safety and dyslipidaemia-correcting efficacy of specific interventions discussed in the guidelines developed for the general population.

After reviewing all available material this Work Group agreed that haemodialysis patients should in principle be treated according to the recommendations of the expert panels of the Joint European Societies on prevention of coronary heart disease or the National Cholesterol Education Program (NCEP) [7–9]. A high-risk strategy should be applied using the recommendations targeting patients with known cardiovascular disease and similar to diabetes, end-stage renal disease (ESRD) was considered to be a coronary risk equivalent. In the absence of data from randomized trials, it can only be assumed that the interventions recommended by the various guidelines will similarly reduce vascular disease in patients with kidney disease and on haemodialysis. Although the concept of accelerated atherosclerosis has been widely accepted since it was first published by Lindner *et al.* in 1974 [17] members of the Work Group clearly express to the readers of these guidelines, that they recommend lipid-lowering treatment despite the absence of evidence in haemodialysis patients that the risk of cardiovascular death is reduced by reducing lipid levels.

Prevalence and type of dyslipidaemia

The prevalence of dyslipidaemia in ESRD is greater than in the general population [18,19]. Haemodialysis

patients exhibit a characteristic dyslipidaemia consisting of hypertriglyceridaemia and low high-density lipoprotein (HDL) cholesterol levels [20,29]. Very low-density lipoprotein (VLDL) cholesterol is typically increased; however, levels of total and low-density lipoprotein (LDL) cholesterol usually are normal or may even be low [30–34]. This pattern further translates into the most characteristic feature of the ESRD-associated dyslipidaemia represented by an accumulation of triglyceride-rich lipoproteins (VLDL-remnants) [22] and intermediate-density lipoproteins (IDL) [29,31]. Furthermore, qualitative changes take place in LDL with a predominance of the small dense LDL (sdLDL) phenotype [34–38]. The overall pattern is best described by an accumulation of apolipoprotein B-containing triglyceride-rich lipoprotein particles containing C-III and (a) or by lipoprotein Bc particles [27,28,39–41]. A defect in postprandial chylomicron-remnant clearance has been described as well [22,42].

Atherogenicity of dyslipidaemia

Growing evidence suggests that all of the components of this type of dyslipidaemia (elevated VLDL-remnants, IDL, sdLDL, low HDL cholesterol) are independently atherogenic [43–45]. Together they represent a set of lipoprotein abnormalities that, besides elevated LDL cholesterol, promote atherosclerosis. Triglycerides are physiologically linked to sdLDL and low HDL concentrations and it is likely that the increased sdLDL contributes to the atherogenic risk for hypertriglyceridaemia [5,46,47]. Atherogenic levels of sdLDL were found in ESRD patients with triglycerides >177 mg/dl [34]. The accumulation of these lipoprotein particles contributes to a so-called atherogenic lipoprotein phenotype. A similar type of dyslipidaemia is also seen in the general population and is called atherogenic dyslipidaemia, which frequently occurs in patients with premature coronary heart disease and appears, in the absence of elevated LDL cholesterol, to be an independent atherogenic lipoprotein phenotype [48]. Most patients with atherogenic dyslipidaemia are insulin resistant and many also have an elevated serum apolipoprotein B. Several theories have been proposed regarding the cause of the increase atherogenicity. The primary metabolic defect is believed to be defective catabolism of triglyceride-rich lipoproteins (primarily VLDL) by the enzymes, lipoprotein lipase [49] and hepatic lipase [50]. Lipid peroxidation products are elevated in plasma [51] but appear not to be generated during haemodialysis [52]. A defect in cholesterol transport has been reported [53] probably due to alterations in CEPT and LCAT activities [54–56]. In respect to mechanism for sdLDL accumulation the suggested causes include: (i) decreased affinity for the LDL receptor [57] with increased clearance via the scavenger receptor [58]; (ii) increased susceptibility to oxidation and glycation, partly as a result of longer residence time in the circulation [59]; (iii) increased transcapillary

permeability and filtration by the endothelium because of smaller size [60]; and (iv) greater affinity for binding to extracellular matrix such as arterial wall proteoglycans [61].

Assessment of the atherogenic risk by serum lipid determination

The finding of an increased prevalence of atherogenic levels of VLDL-remnants [22,62,63], IDL cholesterol [62,64,65], and sdLDL [34–37], in the context of normal plasma total and LDL cholesterol highlights the need to look beyond the basic assessment of plasma concentrations of total and LDL cholesterol when assessing the cardiovascular risk posed by dyslipidaemia in the haemodialysis population. However, measurements of these atherogenic lipoproteins are not available for routine laboratory evaluation at the present time. There is a strong correlation between plasma triglycerides and sdLDL concentrations, highlighting the physiological role of triglycerides in sdLDL formation and its possible use as a surrogate marker. Triglyceride levels > 177 mg/dl (2 mmol/l), used to identify patients with sdLDL, had a sensitivity of 86% and a specificity of 79% [34]. Peroxidative modification, particularly VLDL, also takes place in haemodialysis patients [66,67].

Dyslipidaemia and atherosclerotic vascular disease

Lipid abnormalities have been suggested as a major cause of vascular disease in haemodialysis patients and reviews have focused on the subject of renal failure, dialysis, and dyslipidaemia [68–70]. A number of studies have examined the relationship between various lipid parameters and the presence of clinically apparent atherosclerosis in individuals receiving haemodialysis therapy [19,68,71–73]. These trials have been cross-sectional in nature, including only small numbers of patients, and have failed in part to distinguish atherosclerosis-related events from other forms of cardiovascular disease. Studies also have failed to control for other risk factors and have assessed only total plasma lipid levels rather than the lipoprotein disturbances, which characterize the uraemic dyslipidaemia. It is, therefore, not surprising that the conclusions have been conflicting [74]. In the largest and longest study to date, 419 dialysis patients were followed prospectively over a 21-year period during which time 49% died of cardiovascular disease and 23% experienced fatal or non-fatal ischaemic events. Smoking, hypertension, and hypertriglyceridaemia were identified as independent risk factors for ischaemic cardiovascular disease [75]. In contrast, several smaller cross-sectional studies have failed to find an association between elevated triglycerides and complications resulting from vascular disease [74]. However, in a group of 196 diabetic patients receiving haemodialysis, elevated cholesterol levels with high LDL to HDL ratios were associated with an increased risk of cardiac death during a 45-month follow-up

period. Hypercholesterolaemia was more common in the diabetics than in matched non-diabetic dialysed controls [76]. Lipid measurements were done when patients entered renal replacement therapy. In this respect it is of note that serum cholesterol concentrations decline with time on dialysis [77]. Most cross-sectional studies with longitudinal follow-up have also failed to demonstrate that plasma total- and LDL cholesterol and triglycerides are associated with an increased cardiovascular mortality in haemodialysis patients [78]. There are no longitudinal studies reported for large numbers of patients followed from the start of dialysis, which unravel the degree of cardiac risk with the various lipid abnormalities prevalent in chronic uraemia.

The paradox of cholesterol in ESRD

Prospective observational studies in the general population have shown that the relation between risk of coronary artery disease and blood cholesterol is roughly log-linear. However, inverse associations were observed among haemodialysis patients between blood cholesterol and all-cause [79] or cardiovascular [80] mortality. The relationship between serum cholesterol and mortality has been described as ‘J-shaped’ and the risk of death is 4.3 times greater in haemodialysis patients with serum cholesterol < 100 mg/dl (2.6 mmol/l) than in those with values between 200 and 250 mg/dl (5.2–6.5 mmol/l) [79]. This phenomenon is known as confounding by disease or reverse causality. Concomitant chronic illnesses that induce a compensatory decrease in cholesterol synthesis are also associated with an increased risk of death, producing artefactual negative associations between cholesterol and mortality [81,82]. This effect may limit the extent to which standard observational studies can identify the true impact of serum cholesterol on the development of vascular disease in such populations [83].

Age and lipid lowering

Because cholesterol and LDL cholesterol levels are normal in most haemodialysis patients, coupled with the lack of long-term lipid-reducing studies in this population, the debate continues about the role of lipid-reducing therapy in ESRD, particularly about who should be targeted [84]. Most of haemodialysis patients today are of older age. Trials with HMG-coenzyme A (CoA) reductase inhibitors have included sizable numbers of older persons, mostly in the age range of 65–75 years. In these trials, older persons showed a significant risk reduction with HMG-CoA reductase inhibitors therapy [85]. Thus, no hard-and-fast age restrictions appear necessary when selecting persons with established coronary heart disease for LDL lowering therapy. On the other hand, concomitant illness, general health status, and social issues, may influence treatment decisions and may suggest a more conservative approach.

Further studies and research in uraemic patients are required to assess the risk posed by abnormal lipoprotein particles in this population and the role of lipid-reducing agents in a population with dyslipidaemia and the atherogenic lipoprotein phenotype rather than hyperlipidaemia [86,87].

Guideline VII.2.1

A. All patients should have total cholesterol, triglycerides, and HDL cholesterol measured at presentation, 3 months after beginning of haemodialysis treatment and 6 monthly thereafter.

B. LDL cholesterol should be calculated by the Friedewald formula when triglycerides are <400 mg/dl (4.56 mmol/l).
(Evidence level: B)

C. For triglycerides between 400 and 800 mg/dl (4.56–9.12 mmol/l) direct LDL measurements should be done.
(Evidence level: B)

Commentary on Guideline VII.2.1

Evidence suggests that each of the above dyslipidaemias is associated with vascular disease in the general population and treatment may reduce the risk of vascular disease [7,8]. Measurements are readily available in most clinical chemistry laboratories. As a result of biological and laboratory variation in cholesterol and triglyceride measurements, a reliable assessment of these parameters in each individual requires at least three measurements carried out on three separate samples [8]. Because of further variations in extracorporeal treatment modalities (see Guidelines III.1 and V.2), only a complete plasma lipid profile should be ordered each time dyslipidaemia assessment is recommended. Changes in therapy or other conditions that may affect dyslipidaemia may make more frequent measurements necessary [7,88].

The Friedewald formula is valid in dialysis patients and is sufficiently accurate ($r=0.95-0.97$ calculated LDL vs measured LDL) [89] to allow the determination of LDL cholesterol in the vast majority of the patients [89] (Friedewald LDL cholesterol = total cholesterol – (HDL cholesterol + triglyceride/5)) [20]. Approximately 20% of haemodialysis patients have total triglycerides >400 mg/dl (4.56 mmol/l) [89]. As in other forms of primary or secondary hyperlipoproteinaemias, other methods should be used to measure LDL cholesterol when triglycerides are >400 mg/dl. Direct LDL measurement, lipoprotein electrophoresis or, rarely available, analytical ultracentrifugation should be performed. When triglycerides are >800 mg/dl (9.12 mmol/l) LDL measurement is not recommended.

Guideline VII.2.2

A. All blood collections for lipid screening should be performed, whenever possible, on patients in the fasting state. When screening for dyslipidaemia is done, blood should be drawn immediately before or at least 12 h after a regularly scheduled haemodialysis treatment.
(Evidence level: C)

Guideline VII.2.3

A. Patients should have a complete lipid profile measured every 6 weeks during the initiation phase of lipid lowering intervention. When target levels have been met the frequency can be reduced to every 4–6 month.
(Evidence level: C)

Commentary on Guidelines VII.2.2 and VII.2.3

There is some evidence that the haemodialysis procedure acutely alters lipid levels, in particular triglyceride and free fatty acid levels [90] (see Guidelines II.1 and V.2). As most studies linking dyslipidaemias to vascular disease have measured lipid levels prior to the haemodialysis procedure, screening should be done at this time. Changes in therapy or other conditions that may affect dyslipidaemias may make more frequent measurements necessary. Blood obtained from either fasting or non-fasting individuals can be used for total cholesterol and HDL cholesterol analysis [88].

Guideline VII.2.4

A. Any patient with elevated LDL cholesterol or other forms of dyslipidaemia (elevated total cholesterol and triglycerides and/or low HDL cholesterol) should undergo clinical or laboratory assessment to rule out other secondary causes such as glucose intolerance, hypothyroidism, obstructive liver disease, alcohol abuse, or drugs that decrease HDL cholesterol.
(Evidence level: B)

Commentary on Guideline VII.2.4

Additional secondary disorders include drugs that increase LDL cholesterol and decrease HDL cholesterol (progestins or anabolic steroids) [91,92]. It is particularly important to mention anabolic steroids, which are used for treatment of renal anaemia in countries where erythropoietin is not widely available due to economic constraints. The use of anabolic steroids and the benefits of raising the haematocrit should be outweighed against the potential risk originating from several forms of dyslipidaemia and possible deteriorating vascular disease [91]. Although

lipoprotein(a) (Lp(a)) decreased in one study, triglycerides increased and in most women receiving nandrolone decanoate, mild hirsutism, and voice change is experienced [93]. Antihypertensive or immunosuppressive medications (corticosteroids) may cause superimposed secondary dyslipidaemia.

Guideline VII.2.5

A. Screening for dyslipidaemia should not be performed after surgery or during conditions, which may acutely affect the lipid profile.

(Evidence level: B)

B. Patients without any comorbid conditions and a low total cholesterol (<150 mg/dl; 3.9 mmol/l) should be investigated for possible nutritional deficits.

(Evidence level: B)

Commentary on Guideline VII.2.5

Any illness is defined as an acute infection, diarrhoea, or a vascular accident, such as myocardial infarction. This condition may also include any condition necessitating the arrest of food intake. In patients admitted to the hospital for a major coronary event, LDL cholesterol should be measured on admission or within 24 h [7]. This value can be used for treatment decisions. LDL cholesterol begins to decline in the first few hours after a vascular event and is significantly decreased by 24–48 h and may remain low for many weeks. Thus, the initial (>24 h) LDL cholesterol level obtained in the hospital may be substantially less than usual for the patients. Infection is accompanied by an acute-phase reaction. Activated acute phase and high levels of circulating cytokines, such as interleukin-6 lower cholesterol levels [94,95]. Low or declining serum cholesterol concentrations are predictive of increased mortality risk [79,80,96–98]. Hypocholesterolaemia is associated with chronic protein-energy deficits and/or the presence of comorbid conditions, including inflammation. Cholesterol is influenced by the same comorbid conditions, such as inflammation, that affect other nutritional markers (e.g. serum albumin) [99].

Guideline VII.2.6

A. Patients with elevated LDL cholesterol (100–129 mg/dl; 2.6–3.4 mmol/l) should be treated to achieve LDL cholesterol <100 mg/dl.

(Evidence level: C)

B. Treatment beyond LDL cholesterol lowering should be initiated in patients with triglycerides \geq 180 mg/dl (2.0 mmol/l).

(Evidence level: C)

Commentary on Guideline VII.2.6

Research from experimental animals, laboratory investigations, epidemiology, and genetic forms of hypercholesterolaemia indicate that elevated LDL cholesterol is a major cause of vascular disease [100]. In addition, recent clinical trials robustly show that LDL cholesterol-lowering therapy reduces risk of vascular disease in the general population [95,101]. For these reasons this Work Group decided to extrapolate, at least in part, the data to the high-risk group of haemodialysis patients and to adopt elevated LDL cholesterol as the primary target of cholesterol-lowering therapy. However, targeting LDL cholesterol alone may not be appropriate as elevated LDL cholesterol is not the feature of lipid abnormalities complicating uraemia.

Patients are automatically considered to have coronary heart disease equivalents and, therefore, are at the highest risk for developing vascular disease. They should have no major contraindications to therapy, and no illness that makes prevention and/or treatment of vascular disease unlikely to be beneficial. Lipid-lowering drugs should be administered to achieve LDL cholesterol and non-HDL cholesterol target levels irrespective of whether symptomatic ischaemic heart disease is present. LDL cholesterol levels >100 mg/dl (2.6 mmol/l) and non-HDL cholesterol >130 mg/dl (3.4 mmol/l) are treatment-initiation thresholds for drug therapy.

There is little evidence, which suggests that the risk attributable to LDL cholesterol is similar in haemodialysis patients and in the general population but efficacy and safety of treatment for LDL cholesterol with HMG-CoA reductase inhibitors are identical [102,103]. In general, the cut-off points for drug treatment are based primarily on risk–benefit considerations. LDL-lowering therapy greatly reduces the risk for major coronary events and stroke, and yields highly favourable cost-effectiveness ratios. Those at increased risk are likely to get greater benefit [104–106]. Cut-off points for recommended management based on therapeutic efficacy are checked against currently accepted standards for cost effectiveness. Based on the current literature, haemodialysis patients are likely to achieve cost-effectiveness ratios via a reduction of morbidity and subsequent hospitalization episodes [107–110]. However, the latter remains to be demonstrated.

Guideline VII.2.7

A. In patients with LDL cholesterol 100–129 mg/dl (2.6–3.4 mmol/l) or triglycerides >180 mg/dl (2.0 mmol/l) therapeutic lifestyle changes should be initiated, whenever possible.

(Evidence level: C)

B. Patients with dyslipidaemia should have dietary interviews and/or diaries focusing on the type and

amount of fat. Dietary interviews should be repeated in yearly intervals when target lipid levels are not met during concomitant drug therapy.
(*Evidence level: C*)

Commentary on Guideline VII.2.7

Therapeutic lifestyle changes include: (i) reduced intakes of saturated fat and cholesterol, (ii) increased physical activity, and (iii) weight control [7]. However, haemodialysis patients are already subject to specific food and fluid intake restrictions. The introduction of a diet restricted in saturated fatty acids might add nutritional difficulties and the patients may be at a greater risk of developing malnutrition. There are patients where replacement of saturated fat with non-saturated fat dietary sources will have benefits, but these patients should be selected carefully [111]. Diets rich in polyunsaturated fatty acids of fish-oil origin (omega-3) increase the removal of triglyceride-rich lipoprotein-remnants and reduce postprandial plasma lipoprotein of non-renal patients [112]. Eicosapentaenoic acid reduces plasma remnant lipoproteins and prevents *in vivo* peroxidation of LDL in dialysis patients [113]. When patients are selected for dietary therapy, physicians should refer patients to qualified dietitians and nutritionists at all stages of dietary intervention.

Patients on haemodialysis are less active than healthy sedentary controls, and this difference is pronounced in older individuals [114]. There is an association between physical activity and nutritional status [114]. Exercise training may, if tolerated and maintained over a longer period of time, improve the dyslipidaemia as well as the glucose tolerance in selected patients [115–117]. Whether inactivity or vice versa exercise reduces mortality is not known.

Weight control may be appropriate in early renal failure but is risky in advanced stages of renal failure patients because of its danger to cause malnutrition. Optimization of body weight should best be done together with a moderate increase in physical activity. Because of altered body composition in the uraemic state, optimization of body weight should be preferred over reduction of body weight. Haemodialysis patients normally have a reduced mean subcutaneous fat area/body mass index (BMI) and an increased visceral fat area/BMI [118]. Visceral fat accumulation occurs irrespective of BMI and is associated with serum triglycerides [118]. Weight-for-height is a strong predictor of 12-month mortality in male and female haemodialysis patients. An inverse relationship between mortality rates and weight-for-height percentiles is highly significant for patients within the lower 50th percentile of body weight-for-height [119]. Low BMI is associated with increased risk of hospitalization and mortality. For every one-unit increase in BMI over 27.5 and up to 30, the relative risk of dying is reduced by 30% [120,121]. It may be of importance that

patients have overweight on which they draw in cases of inflammatory conditions [122].

Guideline VII.2.8

A. If after 3 months of therapeutic lifestyle changes, LDL cholesterol is >100 mg/dl (2.6 mmol/l) treatment with a HMG-CoA reductase inhibitor should be initiated.

(*Evidence level: C*)

B. If LDL cholesterol goal is not achieved after 6 weeks of treatment the dose of the HMG-CoA reductase inhibitor should stepwise be increased and a lipid profile be repeated after another 6 weeks.

(*Evidence level: C*)

C. If LDL cholesterol goal is not achieved with therapeutic lifestyle changes and optimal treatment with a HMG-CoA reductase inhibitor additional measures should be considered.

(*Evidence level: C*)

Commentary on Guideline VII.2.8

HMG-CoA reductase inhibitors are the most effective drugs to lower LDL cholesterol in haemodialysis patients [102,103,123] and should generally be the agents of first choice. If LDL cholesterol is still >100 mg/dl (2.6 mmol/l), despite optimal treatment with a HMG-CoA reductase inhibitor, additional LDL cholesterol-lowering drug classes and agents should be considered [124]. Nicotinic acid and derivatives lower LDL cholesterol by 5–25% but are likely to cause side effects such as flushing, hyperglycaemia, upper gastrointestinal distress, and hepatotoxicity [7]. Studies investigating the effect of nicotinic acid in haemodialysis patients are sparse [125–127]. Bile acid sequestrants lower LDL cholesterol by 15–30%. They cause gastrointestinal distress and constipation when not taken with considerable amount of fluids. They are contraindicated in dysbetalipoproteinemia including triglyceride >180 mg/dl (2 mmol/l) [7]. They are likely to further increase plasma triglyceride. Therefore, nicotinic acid and bile acid sequestrants are not preferred treatments in haemodialysis patients. Sevelamer hydrochloride, a non-absorbed hydrogel of cross-linked poly (allylamine hydrochloride) is available as a phosphate binder. Short-term favourable effects on the lipid profile have been observed, with a 20–30% decrease in LDL cholesterol, a 5–18% increase in HDL cholesterol, and no change in triglyceride concentrations, presumably related to the binding of bile acids by the compound [128–130].

Liver function tests should be done at a 6-week interval. CK monitoring is mandatory only if muscle symptoms develop. Without a baseline, creatine kinase values are not always conclusive in dialysis patients, so myopathy may be diagnosed clinically before

laboratory assessment. The dosage of HMG-CoA reductase inhibitors is usually as in the normal population.

Guideline VII.2.9

A. Patients with triglycerides >180–499 mg/dl (2.0–5.7 mmol/l), after 3 months of therapeutic lifestyle changes, should be treated with a HMG-CoA reductase inhibitor, to achieve a non-HDL cholesterol <130 mg/dl.

(Evidence level: C)

B. Patients with very high triglycerides (≥ 500 mg/dl) should be treated with a fibric acid analogue with the dose adjusted according to renal function.

(Evidence level: C)

C. In patients with triglycerides >800 mg/dl (9 mmol/l), resistant to any intervention, the administration of fish-oil and/or a switch to low-molecular weight (LMW) heparin as anticoagulant during haemodialysis therapy should be considered.

(Evidence level: C)

Commentary on Guideline VII.2.9

High fasting triglycerides (180–499 mg/dl) are not used as goals of therapy, but they are markers of increased coronary risk and should be treated, in the absence of increased LDL cholesterol [7]. Aside from optimizing weight and increased physical activity, drug therapy should be initiated to achieve non-HDL cholesterol targets. The finding that elevated triglycerides were an independent cardiovascular risk factor in some studies suggests that some triglyceride-rich lipoproteins are atherogenic [131,132]. The latter are partially degraded VLDL, commonly called remnant lipoproteins. VLDL cholesterol can be a target of cholesterol-lowering therapy. The Third Adult Treatment Panel (ATP III) identified the sum of LDL + VLDL cholesterol (termed non-HDL cholesterol (total cholesterol–HDL cholesterol)) as a secondary target of therapy in patients with high triglycerides (180–499 mg/dl; 2.0–5.7 mmol/l) [7]. The goal for non-HDL cholesterol in patients with high triglycerides can be set at 30 mg/dl greater than that for LDL cholesterol on the premise that a VLDL cholesterol ≤ 30 mg/dl is normal. Therefore, non-HDL goal should be <130 mg/dl (3.4 mmol/l). These target levels are more stringent and thus may have greater impact than higher target levels suggested previously in haemodialysis patients [20,133]. Non-HDL cholesterol has been demonstrated to remain one of the strongest predictors for intima media thickness in 897 haemodialysis patients as demonstrated by multivariate Cox regression analysis [134]. Non-HDL cholesterol also turned out to predict aortic atherosclerosis, determined by pulse-wave Doppler sonography, in a cohort of 205 haemodialysis patients [64]. Therefore, non-HDL

cholesterol is an independent factor affecting arterial wall thickening (intima media thickness) and stiffness (pulse-wave velocity) [34,134].

Fibric acid analogues are effective in lowering serum triglycerides and raising HDL cholesterol. The most common adverse effects of drug therapy are myositis and rhabdomyolysis [135]. These adverse effects can, however be minimized by adjusting the dose of the drugs according to the degree of renal function [136,137]. Gemfibrozil, a fibric acid analogue is well tolerated and the parent drug does not exhibit tendency for accumulation and toxicity. Gemfibrozil has recently been shown to reduce cardiovascular mortality in the VA-HIT study, a large scale secondary prevention study, by reducing triglycerides and increasing HDL cholesterol without affecting LDL cholesterol [138]. However, gemfibrozil is not available in some European countries or even is contraindicated in chronic renal insufficiency or if serum creatinine is >6 mg/dl and/or creatinine clearance <15 ml/min. Although the ATP III listed severe renal disease among absolute contraindications for the use of fibric acids [7] this working group felt, together with several reports from the literature [139,140,141] that gemfibrozil can safely be administered in a dose up to 600 mg/day. A very pronounced lengthening of the fenofibric acid plasma decay was observed in both haemodialysis and peritoneal dialysis patients. Fenofibrate should therefore be used, if at all, with great caution in dialysis patients [142].

The ATP III report does not specify a goal for HDL increasing but concedes that treatment of patients with isolated low HDL (<40 mg/dl; 1.0 mmol/l) is reserved for persons with coronary heart disease risk equivalents [7]. Low HDL cholesterol is a strong independent predictor of cardiovascular disease [143]. Interesting new data demonstrate that HDL, in an inflammatory milieu, changes to a proinflammatory molecule [144] lacking effects that protect LDL from being oxidized under certain conditions [145,146]. Similar findings were obtained in haemodialysis patients [147]. Apolipoprotein A-I, the major structural protein in HDL exists in its free form in serum [148,149]. Clearly, HDL composition and HDL antioxidant capacity is altered in haemodialysis patients [150]. Although clinical trial results suggest that increasing HDL will reduce risk, the evidence is insufficient to specify a goal of therapy in the renal population. Therefore, the present working group felt that more research is needed on HDL and inflammation until recommendations for increasing HDL can be given.

Eicosapentanoic acid reduces plasma lipids [151–154] and remnant lipoproteins and prevents *in vivo* peroxidation of LDL in dialysis patients [113]. Only one study is negative, but more important, n-3 fatty acids from fish-oil do not introduce a clinically important risk of bleeding although doubling of bleeding time is apparent [155]. Adjuvant therapy using LMW heparin for anticoagulation during haemodialysis (for further details see Guideline V.2)

or the use of polysulfone or polyamide high-flux dialysis has been shown to ameliorate hypertriglyceridaemia in some, but not all, patients [156–159]. Treatment of renal anaemia with erythropoietin in haemodialysis patients has beneficial effects on plasma lipid concentrations [160].

Guideline VII.2.10

A. Combining a fibric acid analogue with a HMG-CoA reductase inhibitor should be avoided due to the high risk of rhabdomyolysis.

(Evidence level: B)

Commentary on Guideline VII.2.10

HMG-CoA reductase inhibitors are effective and safe drugs to reduce LDL cholesterol [102,103] and are the agents of first choice. Myositis may occur, in rare cases, particularly when high doses and/or combination therapy (HMG-CoA reductase inhibitor and fibric acid analogues) are used. There are no studies in haemodialysis patients on safety and efficacy using combination therapy.

comorbid conditions. Serum phosphorus was an independent risk factor associated with the extent of the IMT of the carotid artery [15].

Vascular calcifications and oral calcium intake. Wall stiffness is directly related to the presence and extent of arterial calcification. Factors associated with increases in arterial wall rigidity are age, duration of dialysis, plasma fibrinogen, and the prescribed dose of calcium that was used as a phosphate-binding agent [163]. In the study of Goodman *et al.* [165] young adult dialysis patients with coronary artery calcification were ingesting nearly twice as much calcium in the form of calcium-containing phosphate-binding agents than those without detectable calcium deposits.

Morphology of the coronary plaque. An ongoing question is whether the morphology of the coronary lesion in the uraemic patient differs from the non-renal patient. Quantitative measurements have demonstrated that the thickening of the media and intima of the diseased coronary artery is more prominent than in the non-renal patient [168,169]. This finding is consistent with previous observations in non-coronary vessels [170]. There is also more pronounced calcification of the plaques which correlates with the mean serum phosphate concentration. X-ray diffraction analyses show that the calcium-containing deposits are hydroxylapatite. Furthermore, the plaques are heavily infiltrated by activated macrophages, but not foam cells [168,169].

VII.3 Hyperphosphataemia and calcium-phosphorus ion product

A study of 6407 ESRD patients has shown that hyperphosphataemia is increasingly important as a risk for mortality [161]. An elevated calcium-phosphorus ion ($\text{Ca} \times \text{P}$) product indicated risk of mortality as well. Patients with a serum phosphate > 6.5 mg/dl (39%), after adjusting for comorbid factors, had a 27% increase in mortality as compared with patients with serum phosphate in the range of 2.5–6.5 mg/dl. Similarly an elevated $\text{Ca} \times \text{P}$ product (20% of patients > 72 mg^2/dl^2) was associated with a 34% increased mortality risk as compared with those with a $\text{Ca} \times \text{P}$ product between 42 and 52 mg^2/dl^2 [161].

Vascular calcifications

Most adult haemodialysis patients (65%) between the ages of 29 and 72 years have electron beam computed tomography (EBCT) evidence of coronary artery calcifications [162]. The data were confirmed by others which showed that nearly 90% of young adults between 20 and 30 years had EBCT documented coronary artery calcification [163–165]. Calcification scores nearly doubled during a follow-up period of 18–24 months [165]. Hyperphosphataemia [165–167] and $\text{Ca} \times \text{P}$ product [165] increase the risk of vascular calcifications and cardiovascular mortality [161]. In the study of Block *et al.* [161] hyperphosphataemia was an independent risk factor for death even after adjusting for established cardiovascular risks and other

Guideline VII.3

A. Serum calcium and phosphate should be measured in routine intervals and obtained immediately before the haemodialysis session starts.

(Evidence level: C)

B. When serum phosphate is elevated consider recirculation and investigate effective duration of dialysis treatment.

(Evidence level: C)

C. The target range of serum phosphorus in dialysis patients should be 0.8–1.8 mmol/l (2.5–5.5 mg/dl) aiming for a normal $\text{Ca} \times \text{P}$ ion product (< 55 mg^2/dl^2).

(Evidence level: B)

Commentary on Guideline VII.3

Shortened survival and excess cardiovascular death of dialysis patients are predicted by hyperphosphataemia and $\text{Ca} \times \text{P}$. Hyperphosphataemia is associated with increased blood pressure, hyperkinetic circulation, increased cardiac work, and high arterial tensile stress [191]. Multiple factors contribute to elevated phosphate and $\text{Ca} \times \text{P}$ [172] and therefore

a multifactorial approach is necessary. Dietary counselling is necessary while ensuring that the patient does not have protein malnutrition. The recommended protein intake is 1.2 g/kg/day and excess protein and phosphorus intake should be avoided. Improved phosphate binder therapy [173] and dialysis efficacy are measures to improve serum concentrations. The change of modality from haemodialysis to haemodiafiltration [174], or more fundamental changes such as increased frequency of haemodialysis sessions (daily dialysis) [175] or prolonged treatment time may be more successful in normalizing serum phosphate [176]. Phosphate concentrations decrease during the first hour of haemodialysis and begin to increase in haemodialysis or at the end of a haemodialysis session, reaching their predialysis values 4 h after haemodialysis [177]. Treatment changes will not, therefore, easily remove more phosphate; nonetheless, inadequate dose, recirculation, and inadequate blood flow have to be excluded. In the presence of diverging results from different populations and numbers and in the absence of any interventional studies target levels for serum phosphate are difficult to determine. Taking into account increasing evidence of a major increase of mortality risk associated with increased serum phosphate, serum calcium and $\text{Ca} \times \text{P}$ product it would be ideal to target phosphate levels as close to normal as possible (0.8–1.5 mmol/l; 2.5–4.6 mg/dl). However, the risk–benefit ratio of an increased dose of phosphate-binders with the risk of increasing serum $[\text{Ca}/\text{Al}]$ and/or costs has to be considered [178].

for several of these new and emerging risk factors at the present time. As these risk factors most likely contribute to vascular risk to varying degrees they can be utilized to guide intensity of risk reduction therapy in selected patients. Although they do, for example, not categorically modify LDL cholesterol goals, their presence can modulate clinical judgement when making therapeutic decisions. Therefore, this working group felt that a new category, of so-called 'recommendations', should be introduced to this section of emerging risk factor where stringent guidelines could not be developed.

VII.4.1 Lipoprotein(a)

Lp(a) is a LDL-like particle containing apolipoprotein B-100 and the highly polymorphic and glycosylated apolipoprotein(a) (apo(a)) [179]. Lp(a) is one of the few risk factors capable of promoting both early and advanced stages of atherogenesis [180]. Prospective studies have shown a clear association between Lp(a) and coronary heart disease in the general population. A subset of genetically determined Lp(a) isoforms, LMW apo(a) phenotypes, emerged as one of the leading risk conditions of advanced stenotic stages of atherosclerosis in the general population [180,181].

Recommendation VII.4.1

A. Lp(a) should be measured in patients with a long life expectancy on renal replacement therapy in 6-month intervals in order to quantify risk for subsequent cardiovascular disease.

(Evidence level: C)

B. In young patients with a long life expectancy on renal replacement therapy and a Lp(a) > 30 mg/dl the apo(a) isoform should be determined.

(Evidence level: C)

Commentary on Recommendation VII.4.1

Individual physician decisions are mandatory to define long life expectancy on renal replacement therapy. Cardiovascular risk calculations in the general populations are done in decade intervals.

Lp(a) plasma concentrations

A consistent elevation in plasma Lp(a) has been observed in haemodialysis patients in large case-controlled studies [182–189]. The plasma Lp(a) level turned out to be an independent risk factor for cardiovascular disease in some [190–194], but not all cross-sectional studies [195,196]. In a large prospective

VII.4 Emerging risk factors

The pathogenesis of cardiovascular damage in chronic renal failure patients is far more complex than in the general population. The risk for cardiovascular disease is also influenced by other factors not included among the major, independent risk factors such as cigarette smoking, hypertension, dyslipidaemia, age, and family history of premature coronary heart disease. In general, among the so-called other risk factors are life-habit risk factors and emerging risk factors. The former include obesity, physical inactivity, and atherogenic diet; the latter consist of lipoprotein(a) (Lp(a)), homocysteine (Hcy), prothrombotic and proinflammatory factors, impaired fasting glucose, and evidence of subclinical atherosclerotic disease [7]. Haemodialysis patients accumulate a considerable number of these new emerging risk factors, also called non-traditional or non-classical, uraemia-related or uraemia-associated risk factors [6]. They are currently under intense investigation in cross-sectional and longitudinal studies in respect to cardiovascular morbidity and mortality. Some of these factors are not modifiable and no intervention studies will be available soon. For these reasons, it is difficult or in some circumstances, impossible to develop valid guidelines

study, an association of high plasma Lp(a) concentrations with vascular disease was demonstrated [189]. In contrast, another prospective study found no difference in Lp(a) concentrations between survivors and non-survivors in a group of 412 diabetic patients on haemo- and peritoneal dialysis [197]. In a recent prospective study, although Lp(a) was significantly associated with the risk of all-cause cardiovascular mortality in univariate Cox regression analysis, it was not an independent risk factor in multivariate analysis [78].

Apo(a) isoforms

An increase in plasma Lp(a) has been identified only in patients exhibiting high-molecular weight (HMW) apo(a) isoforms [184], but this has not been confirmed by others in different ethnic populations [185,186]. LMW apo(a) isoforms were independent and better predictors for coronary artery disease in a prospective follow-up of more than 400 patients over a period of 5 years [195]. The LMW apo(a) isoforms also predicted the risk for vascular disease in a large prospective study [198] and also that for carotid atherosclerosis [199]. It appears that the Lp(a) plasma concentration and the apo(a) size play a synergistic role in advanced atherosclerosis [200].

Apo(a) fragments

Increased plasma free apo(a) fragments appear to account for only a small proportion of increased Lp(a) [201,202]. No association was found between plasma apo(a) fragments and carotid artery plaques on ultrasound in a recent cross-sectional study [203].

Causes for high Lp(a)

Inflammation and nutrition affect the metabolism of Lp(a) and the plasma concentration [204,205]. For unknown reasons, inflammation affected only HMW apo(a) isoforms [78].

Therapeutical aspects

Other than hormonal therapies, such as ACTH [206,207], D-thyroxine [208], and nandrolone [93] no effective treatments to reduce plasma Lp(a) in patients on haemodialysis treatment or in the general population are currently available. Two small studies described a reduction in plasma Lp(a) by the use of nicotinic acid in haemodialysis patients [126,127]. Consequently, there are no large-scale interventional trials available investigating the effects of such treatments on cardiovascular disease in these patients. The use of anabolic steroids raises haematocrit but is also associated with the development of dyslipidaemia. The overall effect on the cardiovascular system in subjects with normal kidney function is not

beneficial although plasma Lp(a) concentrations may be lowered.

VII.4.2 Prothrombotic and proinflammatory factors

Fibrinogen

Fibrinogen is an acute-phase protein, which affects blood coagulation, blood rheology, platelet aggregation, and vascular wall changes. Mean plasma concentrations increase steadily during life, are greater in women than in men, and are influenced by race [209]. An association between plasma fibrinogen and sub-clinical atherosclerotic disease has been reported in cross-sectional studies [209,210]. Prospective observational studies have demonstrated that elevated plasma fibrinogen is an independent risk factor for cardiovascular disease in the general population and that fibrinogen is pathophysiologically related to vascular disease [211,212]. In meta-analysis the overall odds ratio for fibrinogen was 2.3 (95% confidence interval 1.9–2.8) when the upper tertile levels were compared with the bottom tertile [211]. When corrected for other cardiovascular risk factors, the association between fibrinogen and vascular disease remains statistically significant. Fibrinogen was also identified as a risk predictor for the recurrence of vascular disease event and myocardial infarction in longitudinal studies [209,213]. Associations of fibrinogen with quantity of coronary artery calcification measure by EBCT have been demonstrated [214]. Conflicting data were reported about the association between the β -fibrinogen G/A-455 polymorphism and the occurrence of vascular disease [215,216]. Therapeutic modalities that selectively reduce fibrinogen levels are not yet available. Interventions that are known primarily to have other actions on the cardiovascular system such as weight reduction, regular exercise, smoking cessation, and bezafibrate [209,217] reduced plasma fibrinogen. The Bezafibrate Infarction Prevention (BIP) Study observed an 11% decrease during treatment of bezafibrate in patients with coronary heart disease [217]. Therefore, it is possible that the benefits of reducing cardiovascular disease observed in the Bezafibrate Coronary Atherosclerosis Intervention Trial (BECAIT), which was independent of lowering LDL cholesterol, could be partially attributed to the reduction in plasma fibrinogen [218].

Recommendation VII.4.2

A. Determination of plasma fibrinogen, as a marker of myocardial damage and activated acute-phase response, is recommended at 6-month intervals to appropriately assess cardiovascular disease risk.
(*Evidence level: C*)

B. Smokers with plasma fibrinogen > 3 g/dl should vigorously be encouraged to stop smoking in order to decrease plasma fibrinogen.
(Evidence level: C)

Commentary on Recommendation VII.4.2

A consistently marked increase in plasma fibrinogen has been observed in a number of observational studies [78,196,197,219–225]. The β -fibrinogen G/A-455 polymorphism was not shown to markedly increase plasma fibrinogen in 312 patients [85]. The cause of the increased fibrinogen concentration is likely to be related to inflammation [219,226]. Fibrinogen correlates with interleukin-6 and factor VII coagulant activity as well as prothrombin fragment F1+2 a marker of coagulation activation [227]. The association between fibrinogen and ACVD has been evaluated in several cross-sectional and case-control studies, with conflicting results [195,196,219,223]. Similarly, conflicting results have been reported in prospective studies [78,196,197]. In the first two studies, fibrinogen was identified as an independent predictor of cardiac and non-cardiac death in diabetic and non-diabetic patients on haemodialysis [196,197], whereas in the second study it was not [78]. Fibrinogen is not associated with pulse-wave velocity, a marker of arteriosclerosis, at any vascular site [225]. On the other hand, fibrinogen was associated with a high rate of angiographic restenosis in coronary arteries in a mixed group of haemo- and peritoneal dialysis patients [228]. There is no effective treatment known so far to decrease plasma fibrinogen in haemodialysis patients. However, fibrinogen is modifiable by the use of agents such as bezafibrate in the general population [218] and it is inexpensive to measure (the cost is comparable with the cost of a typical lipid profile). It is also reasonable to use the predictive value of fibrinogen in high-risk uraemic patients to intensify the efforts to correct other risk factors.

Oxidative stress

Haemodialysis patients are subjected to more oxidative stress, which is considered to be a causative and fundamental factor in the pathogenesis of cardiovascular disease [229–231]. Oxidative stress is greater in patients with cardiovascular disease compared with those without [232,233]. Although there is strong evidence that patients have comorbidities related to the imbalance between production of oxidants and antioxidant defence, there is disagreement as to what components are affected at the molecular level (lipids, proteins, advanced glycation end-products (AGEs)). Furthermore, the production of free radicals is often local and transitory.

Oxidation and carbamylation of lipoproteins or apolipoprotein B modification of lipoproteins by AGEs, for example, may increase their atherogenicity. As yet, there are no clinical trials to determine whether

treating specific changes in lipoprotein composition or apolipoprotein modification modifies the incidence of cardiovascular disease.

Causes for oxidative stress. The capacity of dialyser membranes to induce leukocyte oxidative activation might contribute to this oxidative stress (for more details see Guidelines III.1 and III.2). Besides potent endogenous (e.g. angiotensin II) and exogenous causes hypothesized so far, multiple factors are involved which have to be proven in future studies. Total antioxidative capacity is increased in haemodialysis patients [234,235] but depletion of key chain-breaking antioxidants may lead to accelerated atherogenesis. It is controversial whether the haemodialysis procedure *per se* is causing enhanced basal oxidative stress [52,236–241] but the dialyser membrane may play a role [236,242].

Therapeutic strategies to reduce oxidant stress. Therapeutic approaches were directed to reduce inflammatory cell activation and to remove inflammatory mediators or to maintain host antioxidant defence. The concepts of sorbent in haemodialysis or sorbent regenerated ultrafiltrate as replacement fluid are outlined in Guidelines III.1 and IV.1. The search for new extracorporeal manoeuvres is ongoing but none to the proposed concepts, such as haemolipodialysis [243], have been investigated in larger number of patients. Dialysis with vitamin E substituted cellulosic membranes are lowering serum markers of oxidative stress [244,245], prevent endothelial dysfunction and decrease the percentage of aortic calcification index as measured by computed tomography (for more details see Guideline III.2). In most studies demonstrating an advantage, vitamin E-coated membranes were compared with cuprophane, the membrane with the strongest capacity to activated complement and leukocytes. Copper-catalysed LDL oxidation kinetics show a prolonged lag-phase for conjugated diene formation when patients are treated with oral vitamin E (500 mg/day) [246,247]. Malondialdehyde-rich LDL is removed more slowly from circulation than LDL from healthy controls. Oral supplementation with vitamin E (500 mg/day) improved LDL clearance from the circulation and reduced the malondialdehyde content of LDL [248]. Administration of vitamin E (800 U/day) or matching placebo to 196 patients with prevalent cardiovascular disease over a median period of 519 days reduced a composite cardiovascular disease endpoint and myocardial infarction but not total cardiovascular disease or mortality [249].

Although antioxidant therapy may be an attractive future approach to reduce cardiovascular disease and mortality and haemodialysis patients might be more sensitive to vitamin E and other antioxidant therapy than patients with normal kidney function such as the Heart Outcomes Prevention Evaluation (HOPE) study participants

[250], this working group did not feel to be prepared, after reviewing the literature, to give specific recommendations for antioxidant therapy at the present time point.

Metabolic waste products

Asymmetric dimethylarginine. Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of endothelial nitric oxide (NO) synthase [251]. ADMA is degraded by the enzyme dimethylarginine dimethylsaminohydrolase (DDAH), which hydrolyses ADMA to L-citrulline and dimethylamine [252]. Activity of DDAH is decreased by oxidized LDL or tumour necrosis factor- α *in vitro* yielding increased ADMA.

ADMA and haemodialysis treatment. ADMA concentration is elevated in patients with ESRD, in part because it is excreted by the kidneys [253,254]. Pre-dialysis ADMA concentrations in haemodialysis patients are ~6-fold greater than those in a control group [255]. Concentrations in this range (up to 10 $\mu\text{mol/l}$) inhibit vascular NO formation by NO synthase in the presence of L-arginine. ADMA is a small substance with a molecular weight of 202 Da and its concentrations decrease significantly during 5 h of dialysis [255,256].

ADMA and cardiovascular disease. ADMA is significantly greater in patients with manifest atherosclerotic disease as compared with those without atherosclerotic disease [255]. ADMA is an independent predictor of intima media thickness and carotid artery cross-sectional area and of a composite index of severity of atherosclerosis. ADMA is also the most powerful predictor of total and cardiovascular mortality in a cohort of 225 patients with ESRD [257]. Reduced NO elaboration secondary to accumulation of ADMA may be a novel and important pathogenic factor for atherosclerosis in chronic renal failure [258].

Advanced glycation end-products

Evidence from the general population. AGEs are a heterogeneous family of known and unknown chemically reactive compounds. They are formed during non-enzymatic glycation and oxidation reactions of proteins [259]. Several structurally characterized AGEs exist *in vivo*, namely pentosidine, carboxymethyllysine, imidazolone, and pyrraline, which are present in free and protein-bound forms [259]. AGEs have been localized on atheromatous arteries from non-diabetic and diabetic patients [260]. However, there are no observational studies or intervention trials examining the relationship between AGEs and ACVD or the effects of reducing AGEs on ACVD in the general population. Therefore, the clinical importance of AGE measurements or treatment in vascular disease prevention cannot be decided at present.

Evidence from patients with renal disease. Markedly elevated serum and tissue AGE concentrations, measured by different methods, have been reported in

case-control studies in uraemic patients [261–263]. This elevation has been shown to be correlated with both the diminution of renal clearance and the presence of oxidative and carbonyl stress observed in such patients [261]. However, whether it is due to the increased generation or the decreased catabolism of AGEs remains largely unknown.

Accumulation of AGEs has been demonstrated in non-diabetic uraemic patients [264–268] and diabetic uraemic patients [264–267]. A single histopathological study has demonstrated the presence of AGEs in glomeruli, in renal arteries, and in tubular cells in diabetic patients, although AGEs were restricted mainly to renal tubular cells in non-diabetic patients [266]. However, there is no observational study examining the relationship between AGEs and vascular or renal disease progression in uraemic patients. Besides vitamin B6 and high-flux haemodialysis, no satisfactory means of reducing AGEs are available for uraemic patients. Aminoguanidine appears not to be the substance for lowering AGEs in chronic renal failure patients [269–271]. Different dialyzer membrane materials have differential effects on high and LMW AGEs [263] (for more details see Guideline III.1).

Conflicting results were described in haemodialysis patients with respect to AGEs and short-term (32 months) survival. Patients with increasing AGEs as determined by carboxymethyllysine and total AGE-fluorescence in serum showed a better survival than patients with low AGE values [272].

VII.4.3 Homocysteine

Hcy is a sulfur-containing amino acid generated by demethylation of the dietary amino acid methionine [273]. Normal values of fasting plasma concentrations of total (t)Hcy are <14 $\mu\text{mol/l}$. An elevated fasting plasma tHcy is a prevalent and graded risk factor for cardiovascular disease in the general population [273]. The results of a meta-analysis, including primarily retrospective observational studies, have suggested that each 5 $\mu\text{mol/l}$ increment in tHcy is associated with a >50% risk for cardiovascular disease [274]. Some prospective observational studies [275–278], but not all [279,280], have confirmed this graded association between tHcy and vascular disease. The relationship between fasting plasma tHcy and overall mortality is established in patients with manifest vascular disease [281]. Hyperhomocyst(e)inaemia is also associated with a greater risk of venous thromboembolic disease [282]. Homocystozity for the C-677-T transition in the methylenetetrahydrofolate reductase (MTHFR) is associated with higher fasting tHcy, but the mutation does not appear to be associated with increased vascular disease in the general population [283,284]. In the general population, supplementation with both 0.5–5 mg folic acid and ~0.5 mg daily vitamin B12 should reduce blood tHcy concentrations by about one-quarter to one-third (e.g. 12 to 8–9 $\mu\text{mol/l}$) [285].

Whether this therapy effectively reduces the incidence of cardiovascular disease is not known.

Recommendation VII.4.3

A. Folate therapy can be administered in order to lower total plasma Hcy. Folate therapy should always be combined with vitamins B6 and B12.

(Evidence level: C)

Commentary on Recommendation VII.4.3

Fasting plasma tHcy concentrations are greater in >80% of haemodialysis patients [195,286,287] as compared with controls. Therefore, screening of tHcy in plasma was considered unnecessary prior to initiation of folate therapy. Fasting tHcy concentrations are greater in the patients homozygous for thermolabile MTHFR genotype mutation than in non-carriers or those heterozygous for the mutation [288]. The aetiology of hyperhomocyst(e)inaemia is believed to result from a combination of reduction of plasma Hcy clearance observed in the uraemic state [289], genetic factors, and dialysis-related factors [290]. Fasting tHcy correlates with vascular disease in two cross-sectional studies [287] and one study to haemodialysis access thrombosis [195,291]. Two recent prospective studies showed an independent association between increased fasting tHcy concentrations and vascular disease in mixed groups of haemo- and peritoneal patients [292,293]. One study showed a correlation of tHcy to IMT [16]. There are no data on the association between MTHFR genotype and vascular disease in haemodialysis patients. However, in another cross-sectional prospective and well-controlled study, patients with a tHcy <24 $\mu\text{mol/l}$ (the median value) had a significantly worse 4-year survival than those with a tHcy greater than the median. These apparently surprising data were explained by a higher rate of malnutrition present in the group with lower plasma tHcy [294]. Another study found no relationship between Hcy and atherosclerotic disease in women [295].

Supplementation of folic acid at a pharmacological dose (2.5–15 mg/day) has been shown to reduce fasting plasma tHcy concentrations by ~30–40% [296–299]. The use of folic acid at 10–15 mg/day did not improve substantially the percentage decrease in fasting plasma tHcy concentrations obtained with folic acid at 5 mg/day [297,300]. Recently, the use of 5-methyltetrahydrofolate or folinic acid has led to a greater decrease in fasting plasma tHcy levels that observed with folic acid supplementation [299], but this issue is controversial [301,302–304]. Neither serine nor betain effectively reduced fasting tHcy levels [305,306]. Pyridoxine supplementation (300 mg/day) had no effect on fasting tHcy levels in a mixed group of haemo- and peritoneal dialysis patients [307].

High-dose folic acid lowers, but fails to normalize hyperhomocyst(e)inaemia in patients on haemodialysis. Whether the decrease of plasma tHcy is effective in reducing cardiovascular disease is also not known. No effect of treatment was observed upon administration of 5 mg folic acid on carotid artery stiffness over a period of 52 weeks in 54 patients [308]. Folic acid is inexpensive and supplementation apparently has no side effects (although long-term data are limited) [299]. As kidney patients are considered to have the highest cardiovascular risk status the opinion of this working group was that the benefits may outweigh the risks and, therefore, use of folate therapy may be recommended in selected patients. For haematological, neurological, and immunological reasons [269] folate therapy should be combined with vitamin B12 (1 mg/day) and vitamin B6 (50 mg/day) [309]. It should be pointed out that randomized controlled trials are required to demonstrate prevention of cardiovascular disease of folate therapy in haemodialysis patients. Whether compliance to necessary and beneficial medications may decrease by increasing the number of tablets remains to be speculative.

VII.5 Microinflammatory state

Inflammation is thought to play a central role in the pathogenesis and outcome of atherosclerosis and cardiovascular events [310]. A number of novel serum markers currently come to the fore as potential tool to quantify an activated acute phase in apparently healthy individuals [311]. Measurements of markers of inflammation, such as baseline C-reactive protein (CRP), a prominent acute-phase protein, has been proposed as a method to improve the prediction of the risk of these events [312]. Increased CRP is a predictor of coronary events in the general population [313]. Familial and genetic determinants influence systemic markers of inflammation including CRP, albumin, and white blood cell count [314]. The heritability of the three determinants is substantial, accounting for up to 35–40% of the variants in these traits in the general population. In haemodialysis patients, serum CRP is 5–10-fold greater than in healthy controls and multiple factors are currently discussed to be involved in this process [315]. Another marker, procalcitonin, may add value to predict outcome in one study [316] but preferentially distinguishes between inflammation and infection in another study [316,317].

Guideline VII.5.1

A. CRP testing should be included in the routine laboratory evaluation for risk evaluation and stratification in stable patients. Measurements should be done at least in 3 monthly intervals.
(*Evidence level: B*)

Commentary on Guideline VII.5.1

CRP measured years before the acute event independently predicts future risk in haemodialysis patients [78,318,319].

Correlations to other acute-phase proteins

Other negative and positive acute-phase reactants, such as albumin, fibrinogen, apolipoprotein A-I, and Lp(a) correlate with CRP and interleukin-6 and several of these proteins may be additional predictors and/or causative factors of the high cardiovascular risk [78,219,320]. Other acute-phase proteins, such as plasminogen activator inhibitor-1 correlates independently with BMI, triglycerides, and Lp(a) in stepwise regression analysis [321].

Possible treatments

CRP may be a more sensitive indicator of morbidity than any other acute-phase proteins including albumin. Extrapolating the data from the studies in apparently healthy men, aspirin in addition to its antithrombotic effect or a HMG-CoA reductase inhibitor in addition to its lipid-lowering effect, may act as potential modifiers of the inflammatory response [322]. There is also evidence that some of the effects of HMG-CoA reductase inhibitors in preventing a second myocardial infarction is due to an anti-inflammatory effect [108–110].

Other predictive values

The presence of inflammation increases erythropoietin resistance and CRP may be a predictor for the dose of erythropoietin needed for treatment of anaemia [323]. CRP predicts future events and hospitalization [107].

Guideline VII.5.2

A. Patients with CRP > 8 mg/l should be screened for silent infection of haemodialysis access grafts, parodontitis or any low-grade infection.

(Evidence level: B)

B. In patients with elevated CRP (> 8 mg/l) biocompatibility of dialyser membrane and haemodialysis fluid quality should be checked (see Sections III and IV).

(Evidence level: B)

Commentary on Guideline VII.5.2

It appears that the causes for high CRP are multifactorial in origin and derive from endogenous or exogenous stimulatory sources (see also above).

Causes for high CRP

The dialysis procedure. The dialysis procedure *per se* is responsible in part for an inflammatory reaction in haemodialysis patients [324]. Lipopolysaccharide, through dialysate contamination, stimulates cells to secrete cytokines and to initiate an inflammatory reaction. Elevated interleukin-6 is predictive for future all-cause and cardiovascular mortality [94].

Effect of membranes. Dialysis with complement activating, cellulosic membranes results in elevated plasma interleukin-6 at the end of the session, which correlates with increased CRP values 24 h after the start of haemodialysis treatment. This induction is not provoked by more biocompatible membranes [325]. Haemodialysis with a polyamide membrane reduced, but did not normalize, CRP to a greater extent than dialysis with a polycarbonate or cuprophane membrane [326].

Dialysate. The use of ultrapure dialysate will lower plasma CRP as compared with conventional dialysis [327].

Vascular access. The vascular access may also be a candidate to maintain chronic stimulation of CRP production. The presence of an arterio-venous graft is associated with low serum albumin [328]. It is advisable not only to check patent fistulas but also clotted haemodialysis access grafts.

Other, endogenous factors. Compelling evidence now exists that dialysis patients are exposed to enhanced oxidative stress [229,231]. Oxidative stress is initiated by the generation of free oxygen radicals mainly in tissue and probably also in the circulation. The most potent and so far best investigated O₂-stimulating proteins are modified lipoproteins, mainly oxidized (ox)-LDL. A similar and comparable inflammatory milieu may be created by high serum concentrations of AGEs or Hcy. Both stimulators, oxLDL and AGEs, are potent generators of oxygen free radicals *in vitro* via NADP/NADPH-dependent process. Oxidative or carbonyl stress may stimulate cells and the endothelium to produce interleukin-6 which in turn activates the liver to secrete CRP and other acute-phase proteins such as fibrinogen and Lp(a).

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