Optimization of Hypolipidemic and Antiplatelet Treatment in the Diabetic Patient with Renal Disease

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Abstract. Because diabetes confers a very high risk of cardiovascular morbidity and mortality, an aggressive hypolipidemic and antiplatelet treatment has been strongly recommended in the whole diabetic population. In particular, patients who have diabetes should be considered in “secondary prevention” even before presenting cardiovascular events, because diabetes is a “coronary heart disease equivalent.” Furthermore, because renal failure is a cardiovascular risk factor per se, patients with diabetes and renal disease present an even greater risk for atherosclerotic vascular events and should be treated even more intensively with hypolipidemic and antiaggregating drugs: the presence of renal impairment does not justify a nihilist therapeutical approach, even if appropriate cautions are mandatory. Finally, dyslipidemia contributes to the deterioration of renal function, a phenomenon potentially prevented by hypolipidemic therapy.

Large epidemiologic studies show that patients with diabetes present a high risk for cardiovascular morbidity and mortality (1,2) and that diabetes tremendously increases the risk conferred by the other cardiovascular risk factors (3,4), justifying a particularly aggressive therapeutic policy.

Recommendations for Hypolipidemic and Antiaggregating Therapy in Diabetes

The Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) (5) states that diabetes is a “coronary heart disease (CHD) equivalent,” because it confers a high risk for new CHD events within 10 yr, in part owing to its frequent association with multiple cardiovascular risk factors. Furthermore, because people who have diabetes and experience a myocardial infarction have an unusually high death rate either immediately or in the long term, a particularly intensive prevention strategy is warranted. People with CHD or CHD equivalents—such as patients with diabetes—have an LDL cholesterol goal <100 mg/dl and should be treated with intensive lifestyle therapy, maximal control of the other risk factors, and LDL-lowering drugs if baseline LDL cholesterol is ≥130 mg/dl. Lifestyle changes to avoid CHD events consist of increased physical activity, weight reduction, and the following dietary advice: (1) total calorie intake chosen to attain/maintain a desirable body weight and to prevent weight gain; (2) daily total fat intake 25 to 35% of total calories: (a) saturated fats (<7% of total calories) and cholesterol <200 mg/dl, (b) polyunsaturated fat up to 10% of total calories, and (c) monounsaturated fat up to 20% of total calories; (3) daily carbohydrate intake 50 to 60% of total calories (predominantly from foods rich in complex carbohydrates, including grains, fruits, and vegetables); (4) daily fiber intake 20 to 30 g/d; and (5) daily protein intake 15% of total calories.

The recommendations of NCEP/APT III have been considered in the recent Position Statement of the American Diabetes Association (ADA) focusing on Management of Dyslipidemia in Adults with Diabetes (6). The pharmacologic recommendations, however, are even more aggressive. Taking into account the results of clinical trials of lipid lowering in patients with diabetes, the ADA states that (1) the LDL goal is set at <100 mg/dl; drugs should be initiated with LDL concentrations ≥130 mg/dl in the absence of coronary, peripheral, and cerebral vascular diseases and at LDL concentrations ≥100 mg/dl depending on the clinician’s judgment; (2) the decision to start a pharmacologic treatment for hypertriglyceridemia is set between 200 and 400 mg/dl depending on the clinician’s judgment; (3) in patients who show elevated concentrations of both LDL cholesterol and triglycerides, reduction of LDL cholesterol is the first priority; and (4) recommendations concerning lifestyle (moderate exercise, weight reduction, and diet) are similar to those of NCEP/ATP III (5): a particular emphasis is given to glycemic control and moderation of alcohol intake for the correction of hypertriglyceridemia.

As far as hypolipidemic drugs are concerned, the ADA considers as first-line agents statins for LDL cholesterol lowering and fibric acid derivatives for triglyceride lowering and as second-line agents bile acid–binding resins for LDL cholesterol lowering and nicotinic acid for LDL and triglyceride lowering, underlining that no clinical trial has been carried out with the second-line agents in patients with diabetes and that
nicotinic acid worsens glycemic control and bile acid–binding resins increase triglyceride levels (6).

Finally, a position statement of the ADA on Aspirin Therapy in Diabetes (7) gives the following recommendations: (1) use aspirin therapy as a secondary prevention strategy in men and women who have diabetes and evidence of large vessel disease; (2) consider aspirin therapy as a primary prevention strategy in high-risk men and women with type 1 or type 2 diabetes; this includes diabetic subjects with the following: (a) a family history of coronary artery disease, (b) cigarette smoking, (c) obesity, (d) albuminuria (micro or macro), (e) dyslipidemia (cholesterol >200 mg/dl, LDL cholesterol ≥100 mg/dl, HDL cholesterol <45 mg/dl in men and <55 mg/dl in women, triglycerides >200 mg/dl), and (f) age >30 yr. Other points are the following: (1) clopidogrel may be considered as a substitute in case of aspirin allergy, and (2) agents that block a key platelet receptor (GPIIb/IIIa) are under study.

According to these recommendations (5–7), patients with diabetes and renal disease should (1) be treated with an adequate lifestyle, (2) be treated with aspirin already in primary prevention (because they present both diabetes and albuminuria (micro or macro), and (3) be treated with hypolipidemic drugs if LDL cholesterol is ≥130 mg/dl in the absence of vascular complications or ≥100 mg/dl in their presence or if triglycerides are >200 or >400 mg/dl according to individualized clinical evaluation. The hypolipidemic drugs should be statins if the main lipid abnormality is LDL cholesterol elevation; fibrates are contraindicated if renal disease is moderate or severe. The association between statins and fibrates should not be considered because the risk of myositis is inappropriately high in patients with renal disease.

Why should hypolipidemic and antiaggregating therapy be optimized in patients with diabetes and renal disease? Do they need particular cautions before prescribing some drugs? We will answer to these questions in the following paragraphs.

Renal Disease Is a Cardiovascular Risk Factor “Per Se”

When type 2 diabetes is complicated by nephropathy, the cardiovascular risk increases dramatically; in particular, in patients with micro- or macroalbuminuria, it is approximately two to four times higher than in normoalbuminuric patients (8). Actually, an increased albumin excretion rate is not only the earliest manifestation of diabetic nephropathy but also a strong predictor of cardiovascular morbidity and mortality to be included in cardiovascular risk charts (9). The increased risk could be attributed to the fact that microalbuminuria is a marker of generalized endothelial dysfunction, accompanied by a relevant cluster of cardiovascular risk factors, as we recently confirmed in a cohort of patients with type 2 diabetes (10).

The cardiovascular risk increases further with the impairment of renal function. A study carried out by analyzing 3106 patients who were followed up after myocardial infarction at the Mayo Clinic in the 1988 to 2000 period and stratified by kidney function showed that even slight renal function reduc-

Lipid Abnormalities in Diabetes and in Renal Disease

Type 2 diabetes presents a type of dyslipidemia, known as “diabetic dyslipidemia,” characterized by (1) elevation of serum VLDL triglycerides; (2) lowering of HDL cholesterol; (3) excessive postprandial lipemia, as a result of the increased concentrations of VLDL and chylomicron remnants; (4) a preponderance of small, dense LDL (LDL phenotype pattern B); and (5) a preponderance of small, dense HDL (17,18). Its pathogenesis could be summarized as follows (17,18): (1) an enhanced lipolysis as a result of impaired insulin action causes an increased free fatty acid availability to the liver, with an increased VLDL synthesis; (2) a defect in the lipoprotein lipase (LPL) activity—an enzyme regulated by insulin—causes a decreased catabolism of both exogenous (chylomicrons) and endogenous (VLDL) triglyceride-containing particles that remain in circulation for longer periods, together with their remnants; (3) consequently, there is an increased transfer of cholesterol esters, resulting in triglyceride-rich LDL, that are the substrate for the hepatic lipase, usually elevated in type 2 diabetes, with the final end product of small, dense LDL; and (4) the elevation of plasma triglycerides and the reduced ratio between LPL and hepatic lipase causes an enhanced catabolic rate of HDL in circulation. These alterations are mainly due to a defective action of insulin on different steps of lipoprotein metabolism and therefore to insulin resistance (17,18).
Both remnants and small, dense LDL are very atherogenic; in particular, (1) remnants are smaller in size, more dense, and more atherogenic than larger triglyceride-rich lipoproteins (19); they promote lipid accumulation in macrophages, stimulate whole-blood platelet aggregation, and impair endothelium-dependent vasodilation, a phenomenon strictly correlated with endothelial dysfunction (20); and (2) small, dense LDL show a decreased binding capacity to LDL receptor, an increased affinity for cell surface binding sites and for arterial wall proteoglycans—which account for an enhanced penetration into the intima—and an increased susceptibility to oxidation; for all of these reasons, they have been strictly associated with the pathogenesis of both endothelial dysfunction and atherosclerosis (21,22) and have been strongly correlated with the risk of coronary artery disease (23,24). It is interesting that these alterations are even more severe in patients who have diabetes and nephropathy, both micro- and macroalbuminuric. In particular, the amount of albuminuria is closely associated with the average LDL particle size in type 2 diabetes, also independent of plasma triglyceride concentrations (25), and remnant lipoproteins are increased in patients who have type 2 diabetes and microalbuminuria (26).

Dyslipidemia is a major risk factor for atherosclerosis not only in the first stages of diabetic nephropathy but also in ESRD (27). Patients who have ESRD—also independent of diabetes—present the same cluster of lipid abnormalities that we described as the “diabetic dyslipidemia,” characterized by (1) high triglyceride and low HDL cholesterol concentrations (28); (2) accumulation of “remnant particles” (29), which are strictly linked to the atherosclerotic risk also in patients with renal failure (30,31); and (3) the predominance of small, dense LDL particles (32). Cross-sectional studies show that lipid and apolipoprotein abnormalities are already present in the first phases of renal impairment and worsen as renal dysfunction progresses (33). In particular, hypertriglyceridemia is evident when the GFR is <30 ml/min, but elevations of apo CIII and reduction in the ApoA-1/Apo CIII ratio occur earlier in renal disease, as markers of impaired removal of triglyceride-rich lipoproteins (34): elevated triglycerides, apolipoprotein B, and Apo CIII, an inhibitor of LPL function, all contribute to the progression of atherosclerosis in ESRD (35). Furthermore, patients in ESRD present elevated concentrations of lipoprotein (a), which predicts coronary heart disease in these patients (36) as in the general population (37,38).

Finally, lipoproteins undergo in ESRD modifications that increase their atherogenicity, such as oxidation, carbamylation, and modification by advanced-glycosylation end products (39,40), processes that also occur in diabetes per se (41). Thus, (1) ESRD induces processes similar to those that occur in diabetes, because advanced-glycosylation end products and lipoxidation end products are detectable both in patients with diabetes (42) and in patients without diabetes on hemodialysis (43); and (2) patients who have diabetes and ESRD present an atherogenic lipid profile even more severe than nondiabetic patients with ESRD.

It should not be forgotten that in the presence of nephrotic syndrome, LDL concentrations are not only modified but also increased (44). The presence of a very atherogenic cluster of lipid abnormalities in patients with diabetes and renal disease reinforces the need of a very aggressive lipid-lowering therapy.

### Statins and the Correction of Lipid Abnormalities in Renal Disease

Statins are able to correct lipid disorders and to prevent atherosclerotic lesions also in the presence of renal disease. Recent large trials with subgroups of patients with type 2 diabetes demonstrate that statins are generally well tolerated and reduce the CHD events and all-cause mortality both in the general population and in patients with diabetes. The ADA statement (6) quotes the 4S Trial, carried out with simvastatin (45), and the Care Trial, carried out with pravastatin (46), underlining that therapy with statins may be cost-effective when indirect costs of CHD are taken into account (47). Two more recent trials should be considered: the Heart Protection Study, carried out in both primary and secondary prevention in >20,000 high-risk individuals with usual cholesterol levels, including approximately 6000 patients with diabetes, showed a 25% reduction in vascular events in patients with diabetes on simvastatin (48), whereas the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT), carried out in both primary and secondary prevention in >10,000 ambulatory individuals with LDL cholesterol <189 mg/dl—including approximately 3600 patients with diabetes—randomized to usual care (which could imply statin treatment) and to pravastatin did not show significant effects of pravastatin in the reduction of all-cause mortality or CHD events either in the total cohort or in the type 2 diabetes subgroup (49), probably owing to the modest cholesterol and LDL cholesterol differential between control and treatment groups. For this reason, the ALLHAT-LLT authors concluded that their results emphasize the need of obtaining an adequate reduction in LDL cholesterol in clinical practice when lipid-lowering therapy is implemented. Also including the ALLHAT-LLT, the statin trials, taken together, show a significant 27% reduction of CHD events and a significant 14% reduction in all-cause mortality, associated with an 18% reduction in mean total cholesterol levels (49).

Finally, a trial carried out only in patients with type 2 diabetes showed that atorvastatin reduces total cholesterol, LDL cholesterol, and apolipoprotein B and increases HDL cholesterol and decreases triglycerides—a 25% reduction being achieved already with 10 mg/d—thus correcting all of the abnormalities of diabetic dyslipidemia (50).

But are statins effective also in subjects with renal disease? In short-term studies, they correct lipid changes characterizing chronic renal failure and the nephrotic syndrome (51). A placebo-controlled trial that examined atorvastatin effects in dyslipidemic patients undergoing peritoneal dialysis showed that after 4 wk of treatment, approximately 85% of patients presented an LDL cholesterol value ≤135 mg/dl and that after 16 wk, patients on atorvastatin continued to show reductions of total and LDL cholesterol, triglycerides, and total cholesterol: HDL cholesterol ratio and significant increases of HDL cholesterol when compared with placebo patients (52).
Statins also reduce remnant-like particles (53) that are elevated in ESRD patients. Furthermore, they correct endothelial dysfunction, stabilize plaques, and influence coagulative abnormalities (54). Plaque stabilization is a relevant therapeutic goal, because plaque instability leads to plaque rupture, platelet activation, thrombus formation, and vessel lumen occlusion, the more frequent cause of sudden cardiovascular events (55). Finally, because ESRD is accompanied by an increased inflammatory pattern, pathogenetically involved in atherogenesis (16), statins can be useful also owing to their anti-inflammatory properties (56), maintained in hemodialysis patients (57).

The so-called “pleiotropic effects” of statins “beyond cholesterol lowering” (54,58) are described briefly in the next section. These effects account for the drug influence on cell proliferation, thrombosis, inflammation, endothelial function, and immunomodulation that could play a pivotal role in the control of both atherogenesis and kidney damage.

**Lipids and the Progression of Kidney Damage: The Protecting Role of Statins**

Another link between renal disease and lipid disorders is the observation that hyperlipemia contributes to the deterioration of renal function (59,60). In particular, (1) in hypercholesterolemic rat models, there is deposition of lipids within glomerulus and tubulointerstitium (61); (2) reabsorption of lipids filtered by the damaged glomerulus promotes tubulointerstitial injury (62); (3) mesangial cells, which are similar to vascular smooth muscle cells and respond to the same stimuli (63), express receptors for LDL cholesterol, and both LDL and VLDL promote their proliferation (64,65); (4) LDL-activated mesangial cells oxidize the lipoproteins, rendering them cytotoxic (66); and (5) mesangial cell activation in response to LDL stimulates on the one hand fibronectin and chemotactant synthesis, which leads to enhanced mesangial matrix production and exacerbation of renal scarring, and induce, on the other hand, a further recruitment of inflammatory cells (67). A prospective study carried out on 73 nondiabetic patients with primary chronic renal disease showed that a pivotal role in the progression of renal failure is played by total cholesterol, LDL cholesterol, and apolipoprotein B but not by triglycerides and HDL cholesterol (68). In this light, it is not surprising that a role in prevention of renal damage progression could be played by statins (69).

A meta-analysis of 13 studies—more than half in patients with diabetes—that evaluated the role of lipid lowering in the progression of renal disease in 362 patients demonstrated that lipid reduction has beneficial effects on the decline of the GFR similar to that of converting enzyme inhibitors, the effects on proteinuria being more controversial (70). The authors concluded that, if a randomized trial were to be planned, then 2600 subjects will be needed to reach a sufficient power to examine the impact of lipid reduction on progression of renal disease. This trial, however, would be unethical, because patients with renal disease show so high a cardiovascular risk that statin treatment is mandatory in the presence of hyperlipidemia (71).

As far as diabetic nephropathy is concerned, a kidney protective role of statins has been observed in some (72,73) but not in all of the studies (74). In animal models, statins prevent the development of spontaneous glomerular scarring in the obese Zucker (75,76) and Dahl “S” hypertensive rats (77).

When incubated in vitro, statins reduce proliferation of mesangial cells (78). Furthermore, the statin-induced inhibition of chemotactic factors, growth-promoting cytokines, and matrix components such as collagen and fibronectin (79) could be relevant for kidney protection, whereas the statin-induced improvement of endothelial function that occurs in only 4 wk of treatment could exert potential beneficial hemodynamic effects (80).

Finally, statins reduce T-cell cytotoxicity and might lower the incidence of acute rejection after organ transplantation (81). Thus, statins could protect kidney both by lowering LDL cholesterol and by their pleiotropic effects, likely as a result of isoprenylation processes, and involving antiproliferative effects (82).

It is known that by inhibiting 3-hydroxy-3-methyl-glutaryl CoA reductase activity, statins reduce the synthesis not only of cholesterol but also of a number of nonsterol metabolites derived from the same pathway, in particular of mevalonic acid (83). Phosphorylation of mevalonic acid gives rise to several nonsterol isoprenoids, such as farnesyl pyrophosphate and geranylgeranyl pyrophosphate, which become covalently linked to intracellular proteins and modify their function, a process named “isoprenylation” (84). In particular, farnesyl pyrophosphate and geranylgeranyl pyrophosphate modify posttranslationally some small GTPase proteins, such as Ras and Rho GTPases, which are critically involved in the transmission of signals derived from membrane receptors and modulate renal function by regulating the organization of the actin cytoskeleton, smooth muscle contraction, stress fiber formation, cell migration and cytokinesis, cell proliferation, and protection against apoptosis (85,86). Thus, statins, by inhibiting Rho prenylation and consequently the activation of Rho kinases, could play an important role in reducing kidney damage. It should be underlined that the lovastatin ability to reduce mesangial cell proliferation is prevented by addition of mevalonate (78) and therefore is attributable to the pleiotropic effects of statins. Prevention of Rho GTPases activation by statins has been involved in the simvastatin-induced inhibition of high glucose–induced proliferation of mesangial cells, a phenomenon that plays a pivotal role in the pathogenesis of diabetic nephropathy (87). The authors concluded that these results provide a new rationale for the use of statins in early stages of diabetic nephropathy independent of cholesterol-lowering properties and that statins should be evaluated in the prevention of diabetic nephropathy.

**Chronic Renal Failure and Bleeding Tendency**

Uremia is characterized by an increased bleeding tendency, as it has been reviewed (88). Causes of “uremic bleeding” are (1) platelet abnormalities (e.g., subnormal dense granule content, reduction of intracellular ADP and serotonin, impaired release reaction, enhanced intraplatelet levels of the antiaggregating cyclic nucleotide cyclic AMP, reduced mobilization of
platelet calcium, altered platelet arachidonic acid metabolism, reduced aggregating response to different stimuli, reduced cyclo-oxygenase activity, abnormalities in the fibrinogen binding protein IIb-IIIa; (2) abnormal platelet–vessel interactions (e.g., reduced platelet adhesion, increased vascular formation of prostacyclin, altered von Willebrand factor); and (3) anemia (i.e., altered blood rheology and erythropoietin deficiency). A unifying cause of these abnormalities has been identified in the increased formation of nitric oxide (NO), a molecule deeply involved in the inhibitory control of platelet function (89). The increased NO formation in uremia has been ascribed to accumulation of guanidinosuccinic acid, a guanidine derivative related to L-arginine (88), and to the activation of the inducible NO synthase in neutrophils and in monocytes (90). It has been observed that erythropoietin therapy ameliorates the defective calcium signaling of uremic platelets (91).

It should be mentioned, however, that some researchers found that platelet activation is increased in ESRD patients, with formation of erythrocyte/platelet complexes, and that this phenomenon is aggravated by dialysis (92). Furthermore, recent reports indicate that predialysis patients with chronic heart failure as well as dialysis patients present an activated coagulation system, as indicated by the increased markers of activated plasma coagulation (thrombin-antithrombin complex and prothrombin fragments 1 and 2), and that this is further enhanced by dialysis sessions, which are potentially thrombophilic states (93), also because platelets are activated by the dialysis membranes. Thus, platelet and coagulation function in uremic patients on dialysis could fluctuate in pre- and postdialysis periods.

Chronic Renal Failure and Platelet Antiaggregating Therapy

Antiplatelet therapy prevents death, myocardial infarction, and stroke in high-risk subjects, and in patients with diabetes is associated with a 7% proportional reduction in serious vascular events (94). Aspirin is the most widely used antiaggregating drug: its dose for prevention of cardiovascular disease in patients with diabetes needs to be evaluated further by ad hoc studies (95). At present, low doses of enteric-coated aspirin should be preferred, because they show the lowest side effects (7).

The use of aspirin in patients with chronic renal failure has been debated. As already pointed out many years ago, aspirin increases bleeding time in uremic patients more than in healthy subjects (96), encouraging caution in aspirin prescription and suggesting the importance of a pharmacologic gastric protection.

Another reason of caution is the suspicion that aspirin increases the risk of renal impairment. A study described that aspirin use was associated with a risk of chronic renal failure 2.5 times as high as that for non-users; the risk increased with an increasing cumulative lifetime dose of aspirin and with an increasing average dose during periods of regular use but not with an increasing duration of use (97). Even if the possibility of bias is due to triggering of analgesic consumption by pre-disposing conditions, this recent study opens an old controversy (98).

Owing to all of these problems, antiaggregating agents are administered with the greatest caution in the clinical practice in patients with chronic renal failure. For instance, a survey of >130,000 elderly (≥65 yr old) patients who were hospitalized for myocardial infarction showed that in-hospital aspirin administration decreased from 72 to 65% and 58% according to the initial serum creatinine values of <1.5, 1.5 to 2.4, and 2.5 to 3.9 mg/dl, respectively. It is interesting that 1-yr survival decreased with the increase of creatinine levels, indicating that renal failure reduces the prognosis, whereas 1-mo mortality hazard ratios showed protective effects of aspirin in the three creatinine categories (0.40, 0.45, and 0.52, respectively) (12). The underutilization of aspirin has been considered to some extent to be responsible for the poor cardiovascular prognosis of patients with renal failure, because a consistent age-adjusted mortality rate reduction with aspirin use after myocardial infarction has been observed across all renal function groups (12,99). However, because it cannot be ruled out that patients who did not receive aspirin may have had a poor outcome owing to the comorbidity preventing the use of aspirin, it also has been suggested that further studies are needed to explore the risk-benefit ratios in these high-risk patients (100).

Antilipidemic and Antiaggregating Therapy in Patients with Diabetes and Renal Disease: Firm Points and Controversies

If patients with diabetes are at very high cardiovascular risk simply because they have diabetes (1), then the presence of renal disease confers an additional risk and could need additional reinforcement of the cardiovascular preventive measures: among them, hypolipidemic and antiplatelet therapy. A recent editorial, commenting on the poor cardiovascular outcome of patients with kidney disease and the less aggressive therapy prescribed to these patients, especially when diabetic, owing to the increased risk of iatrogenic effects, stated that “our reticence to use therapies with established benefit during the in-hospital management and after-discharge phase of care in patients with renal failure needs to be reevaluated” (101).

Obviously, no problem exists when subjects present the first stages of diabetic nephropathy, with no or mild renal function impairment and the presence of microalbuminuria. In these patients, all of the above-mentioned recommendations of the scientific societies (5–7) should be reinforced, and all of the appropriate drugs should be administered.

The problems arise when kidney function is moderately or severely reduced. Some recommendations concerning lipid-lowering therapy in these patients were proposed some years ago (51). The safest hypolipidemic drugs are certainly statins, because their tolerability profile is good. Actually, they can be used also in advanced renal failure because of prevalent gastrointestinal excretion (values ranging from 58% for simvastatin to 90% for fluvastatin, with the intermediate values of 70% for atorvastatin and pravastatin) (102). We previously mentioned the satisfactory lipid-lowering results obtained with
atorvastatin in dyslipidemic patients on peritoneal dialysis (52), and we are waiting for the results of an ongoing trial examining whether lowering plasma cholesterol and triglycerides with 20 mg/d atorvastatin will decrease the incidence of cardiovascular mortality and nonfatal myocardial infarctions in 1200 patients with type 2 diabetes on hemodialysis (103). Statins should be used also in transplant recipients without relevant risks of rhabdomyolysis, provided that high doses are avoided in patients who are treated with cyclosporin (104,105).

When triglycerides are elevated and HDL cholesterol is reduced, a low-dose fibric acid derivative has been proposed if reinforced therapeutic lifestyle changes are not enough. These drugs, however, should be avoided in moderate or severe renal failure (51). In this case, the triglyceride-lowering ability of atorvastatin should be used (50,52). Furthermore, the use of fish oils could be considered. The recent recommendations from the American Heart Association concerning omega-3 fatty acids—polyunsaturated components of fish oils—and cardiovascular diseases (106) (1) state that they have been shown to decrease risk for arrhythmias, which can lead to sudden cardiac death, reduce the risk of thrombosis, decrease triglyceride and remnant lipoprotein levels, decrease rate of growth of the atherosclerotic plaque, improve endothelial function, slightly lower BP, and reduce inflammatory responses and (2) recommend that all adults eat fish at least two times a week, that patients with documented coronary heart disease eat 1 g of eicosapentaenoic acid and docosahexaenoic acid (combined) per day via consumption of oily fish or via capsules to be taken after consultation with a physician, and that eicosapentaenoic acid + docosahexaenoic acid supplement may be useful in patients with hypertriglyceridemia. Among the several studies carried out, we quote a recent investigation demonstrating that treatment with these compounds induced a 20% reduction in total mortality and a 45% reduction in sudden death in patients who survived a recent myocardial infarction over a 3.5-yr observation period (107). A small randomized and placebo-controlled trial demonstrated that short-term low-dose supplementation with polyunsaturated fatty acids is safe and able to reduce triglycerides in hemodialysis patients (108).

When both LDL cholesterol and triglycerides are elevated, statins should be considered the best choice, and the combination of statins and fibrates should be avoided, owing to the inappropriately high risk of rhabdomyolysis (51). Among statins, atorvastatin has been considered with attention, owing to its ability to reduce triglycerides and its predominant liver excretion (109). A not yet recommended but likely possible therapeutic option when statins alone are not able to induce an appropriate decrease in triglycerides is to associate fish oils.

Obviously, in the presence of moderate or severe renal failure, clinical and laboratory controls to detect drug side effects promptly should be intensified. Particular attention should be paid to the statin-induced rhabdomyolysis.

But what about the platelet antiaggregating therapy? The ADA advises to prescribe aspirin to all patients with diabetes and micro- or macroalbuminuria (7). A low-dose gastric-coated preparation should be considered at present the safest choice. Also in this case, the problems arise in the presence of ESRD, which *per se* confers an increased bleeding risk (88). A careful evaluation of benefits/risks should be done in these cases. When the final decision is to administer aspirin, the doses should be low, gastroprotection should be prescribed, and a careful monitoring of bleeding should be planned.

In conclusion, patients who have diabetes and renal disease present so huge a cardiovascular risk that an aggressive preventive therapy should be used. The benefits of a multifactorial intervention targeting hyperglycemia, hypertension, dyslipidemia, and microalbuminuria and including aspirin administration have been recently demonstrated by the Steno-2 Study, a clinical investigation carried out in microalbuminuric patients with type 2 diabetes: with a mean follow-up of 7.8 yr, a 50% reduction of both cardiovascular and microvascular events have been demonstrated (110). In this study, statins (atorvastatin in particular) have been used in case of isolated or combined hypercholesterolemia and fibrates in case of isolated hypertriglyceridemia (>350 mg/dl) (110). Obviously, this study does not allow differentiation of the preventive effect of each therapeutic measure but gives new strength to the efforts to optimize the treatment of patients with type 2 diabetes and first phases of renal disease to reduce both the rate of progression of kidney damage and the high cardiovascular risk.

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