Cardiovascular Death in Dialysis Patients: Lessons We Can Learn from AURORA

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Cardiovascular events are the dominant cause of death in patients with ESRD. Until recently, plaque rupture due to atherogenic dyslipoproteinemias was presumed to be a major mechanism of cardiovascular events in dialysis patients. But how reasonable was that hypothesis and was it entirely discredited by the results of 4D and AURORA? This article places the conventional lipids—cholesterol and triglyceride—within the more physiologic framework of the apoB lipoproteins. Viewed from the perspective of atherogenic particle number, the failure of statins to lower cardiovascular mortality in hemodialysis patients *versus* the continuing potential for success in peritoneal dialysis patients becomes comprehensible. In the former, apoB is characteristically not elevated and therefore apoB-lowering therapy can have only limited effect; in the latter, apoB is characteristically high and therefore apoB-lowering therapy might have considerable clinical benefit. Nevertheless, plaque rupture is only one mechanism leading to cardiac death. In addition to those previously noted, a new mechanism is suggested for consideration—recurrent reperfusion injury. The coronaries of dialysis patients are often narrowed, the microcirculation underdeveloped, and the left ventricle hypertrophied—all of these plus transient hypotension could produce severe ischemia followed by reperfusion necrosis. The minor but common elevations of troponin that are so well known yet widely disregarded may be markers of an adverse sequence of events that could each trigger a fatal arrhythmia and tend to reduce left ventricular function. Thus sudden death due to arrhythmia and slow progressive death due to heart failure could be manifestations of reperfusion injury.

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It all seemed so simple, so straightforward, so certain. Cardiovascular disease is the major cause of death in dialysis patients (1,2), dyslipidemia is common in dialysis patients, and statins reduce cardiovascular event rates because they treat atherogenic dyslipidemia; therefore, statin therapy will reduce the abysmally high death rate in dialysis patients. The 4D study and AURORA have brutally contradicted this line of logic (3,4). In neither of these well conducted studies did statin therapy reduce cardiac deaths or major cardiac events. Yet does this mean that statins have no place in the therapy of patients with renal disease? And what does it say about the mechanisms of cardiac death in dialysis patients?

Our purpose is to demonstrate why the outcomes in 4D and AURORA should not have been surprising; to outline where we think lipid-lowering therapy now stands in patients with renal disease; and to identify mechanisms other than plaque rupture, mechanisms not primarily driven by plasma lipids, that could contribute to cardiac death, particularly in dialysis patients. We will start by examining the issue of the relations of VLDL and LDL to the risk of vascular disease.

Until recently, disorders of lipoprotein metabolism were characterized only in terms of the major plasma lipids—triglycerides and cholesterol. Most triglyceride is contained in VLDL particles, whereas most cholesterol is present in LDL particles (5). Elevated LDL cholesterol (LDL C) is unquestionably a potent risk factor for vascular disease, and statins are unquestionably a potent therapy to reduce LDL C and cardiovascular risk. On the other hand, hypertriglyceridemia is much more common than hypercholesterolemia in patients with vascular disease (6,7). Hypertriglyceridemia is also a more frequent finding than hypercholesterolemia in patients with ESRD, particularly in those treated with hemodialysis (HD) (8). Nevertheless, most studies fail to demonstrate that triglycerides are an independent risk factor for vascular disease and, to date, clinical trials have not demonstrated any clear benefit related to lowering of plasma triglycerides. Thus one abnormality—hypertriglyceridemia—appears common, but not necessarily important, whereas the other—hypercholesterolemia—is less common, but indisputably important.

A very different understanding emerges if one examines plasma lipids as lipoprotein particles. This can be done in different ways. The approach we have developed, which can be

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done in all clinical laboratories, is based on lipids and apoB (9). Each VLDL and LDL particle contains one molecule of apoB100 (apoB) (5). Trapping of an apoB particle within the arterial wall is the seminal event that initiates and promotes the maturation of the atherosclerotic lesion that eventually sets off the cascade of events leading to plaque rupture and acute coronary thrombosis, myocardial injury, and death. In this pathophysiological sense, apoB particles are causal factors, not risk factors, for arterial disease.

As illustrated in Figure 1, VLDL and LDL particles can differ substantially in composition (5). The larger the VLDL particle, the more triglyceride it contains; the smaller the LDL particle, the less cholesterol it contains. Because VLDL and LDL are heterogeneous in composition, it follows that neither VLDL nor LDL particle number can be deduced from the plasma levels of triglycerides or LDL C. On the other hand, each LDL particle, like its VLDL precursor, contains one molecule of apoB. Therefore, total atherogenic particle number can be directly estimated by measuring apoB.

With rare exceptions, in any individual, there are approximately 9 times as many LDL particles as VLDL particles (5). Each of these particles has one molecule of apoB, and that means that plasma apoB is driven by LDL apoB. This massive difference in number is the major reason why LDL particles are so much more important in atherogenesis than VLDL particles. Another important reason is that LDL particles are so much smaller than VLDL particles and as such can more easily enter the arterial wall. But does hypertriglyceridemia with a normal LDL C mean that LDL particle number is normal? Not at all; as illustrated in Figure 2, hypertriglyceridemia can be due to a few very large VLDL particles or to a greater number of intermediate-size VLDL particles. The former—hypertriglyceridemia with normoapoB—is associated with few LDL particles compared with the latter—hypertriglyceridemia hyperapoB. In both instances, most of the LDL particles are smaller and denser than normal because they contain less cholesterol ester than normal. This difference in composition is due to exchange of the core lipids, triglycerides, and cholesterol ester and explains why LDL C so often substantially underestimates LDL particle number.

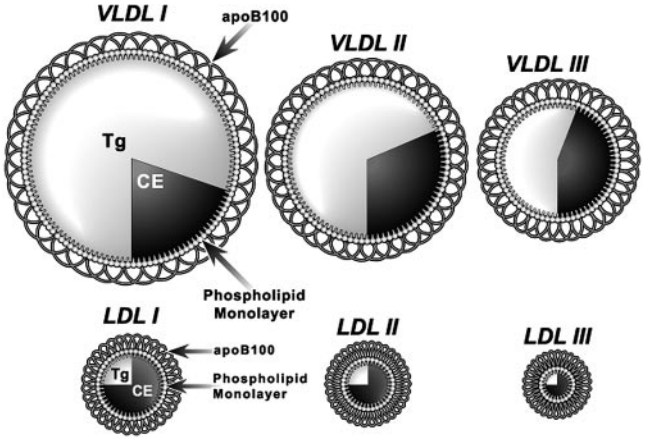

Figure 1. Illustration of the major types of VLDL and LDL particles. Each contains one molecule of apoB100. VLDL particles are triglyceride-enriched whereas LDL particles are cholesterol-enriched. The VLDL particles differ in the amount of triglyceride they contain whereas the LDL particles differ in the amount of cholesterol they contain.

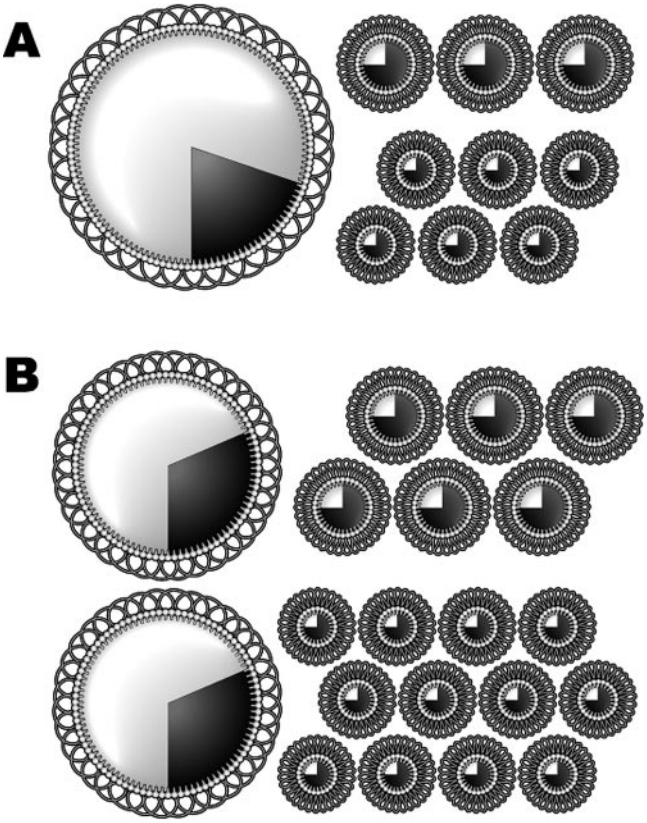

Figure 2. Illustration of the two major mechanisms of hypertriglyceridemia—hypertriglyceridemia due to large, triglyceride-rich VLDL particles or due to increased numbers of VLDL particles with intermediate amounts of triglyceride. In the former, LDL particle number and plasma apoB are normal, whereas in the latter LDL particle number and plasma apoB are increased.

The distinction matters because there is now overwhelming evidence that atherogenic particle number as estimated by apoB is a more effective marker than LDL C of the risk of vascular disease and the adequacy of LDL therapy (5,10,11). The apoB paradigm also explains why risk in hypertriglyceridemic patients is principally due to LDL and therefore why LDL-lowering therapy should be the principal approach to reduce the risk of vascular events due to atherogenic lipoprotein particles.

Other lipoprotein diagnostic approaches have been suggested such as that developed by Alaupovic and his colleagues, which provides a detailed characterization of the apoB particles, and in particular, the triglyceride-rich apoB particles (12). In patients with ESRD, they have confirmed that the number of LDL particles, LDL B, is normal but there is an accumulation of B:C and AII:B:D:E lipoprotein particles in the VLDL and IDL density range (13). Moreover, it has been hypothesized that

increased levels of apoC-III substantially and independently increase the risk of clinical atherosclerosis events (14). Therefore, one explanation for the failure of statin treatment in AURORA could be their limited effect on apoC-III and the triglyceride-rich apoB particles. However, as noted above, we think that it is in fact the number of LDL particles that principally drives the risk in the hypertriglyceridemic patients.

This is a critical point: If apoB is not high, the risk related to LDL particles is not high. Accordingly, the benefit from lowering LDL will not be great. Figure 3 demonstrates the risk due to apoB in the American population on the basis of the results of the Framingham Offspring Study. If subjects are on the plateau phase for values of apoB, even substantial percentage decreases in the level of apoB will not produce substantial absolute differences in event rates. Given that diabetes is such a common cause of renal failure and given that hyperTg hyperapoB is so common in diabetes, it might be presumed that apoB levels would be high in HD patients. However, that is not commonly the case. Patients change in many ways as their renal failure progresses, and modification of their lipid status is just one of them. Considerable previous work has demonstrated that patients with ESRD treated with HD characteristically have elevated triglyceride levels, normal or low LDL C, and normal or low apoB (15–21); that is, their VLDL particles are abnormal in composition but the number of LDL particles is normal or low-normal. Unfortunately, apoB was not included in the published results of AURORA or 4D, but if their patients were representative of patients treated with HD, it is not difficult to understand why so little clinical benefit was observed with statin therapy.

This does not mean that statins are of no benefit in all patients with renal disease. On the contrary, there are several categories of patients with renal disease that are associated with high levels of apoB and in which statin therapy is very likely of substantial clinical value. The first, nephrotic syndrome, is characterized by markedly increased VLDL and LDL particle numbers and therefore by hypertriglyceridemia, hypercholesterolemia, and elevated apoB (8). Although there are no specific clinical trials, given the strength of the relation between apoB and cardiovascular risk, statin therapy aimed at lowering apoB would intuitively be the prudent course. Second, hypertriglyceridemic hyperapoB is the hallmark atherogenic dyslipoproteinemia of type 2 diabetes mellitus (22). Higher apoB levels have also been described in patients with predialysis chronic kidney disease (stages 4 to 5) as compared with healthy controls (23). There is also evidence that at least the initial stages of renal injury manifested by albuminuria can drive plasma apoB to higher levels in patients with type 2 diabetes (19). On the other hand, there is reasonable preliminary evidence that the rate of renal injury is related to plasma apoB and that statin therapy may reduce the rate at which renal failure develops (24,25). Given the prevalence of type 2 diabetes and the frequency of renal failure as a complication of diabetes, confirmation or refutation of these findings should be a high priority.

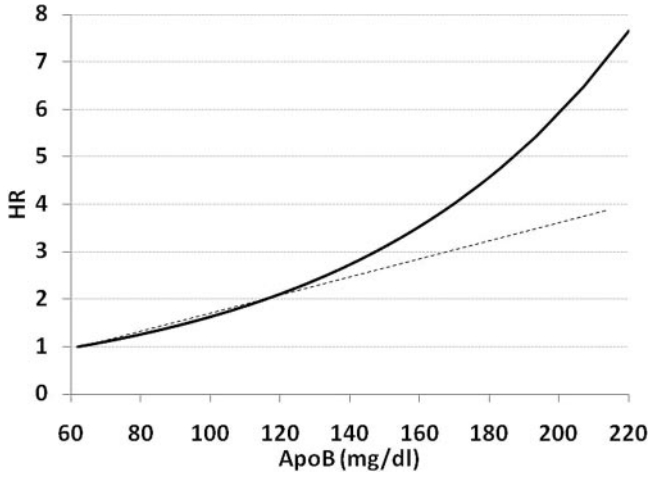

Figure 3. Relation between the concentration of plasma apoB and the risk of cardiovascular events.

Finally, two other clinical groups likely to benefit from statin therapy are ESRD patients with a renal transplant or receiving peritoneal dialysis (PD) as renal replacement therapy. In both groups, elevated apoB, with or without hypercholesterolemia, is common. In the transplant population, dyslipidemic changes are associated with calcineurin and glucocorticoid immunosuppressive therapy (26). On the other hand, the hyperapoB atherogenic dyslipoproteinemia in patients receiving PD almost certainly reflects the effect of dialysis based on glucose-mediated osmotic ultrafiltration and diffusion (15–21). Moreover, it seems reasonable to hypothesize that this atherogenic dyslipidemic pattern in PD patients may explain the loss of their early survival advantage over HD patients (27). Indeed, a recent analysis from the Australian and New Zealand Dialysis and Transplant registry reported that cardiovascular death rates after 1 year on dialysis are significantly higher in PD patients compared with HD patients and that death due to acute myocardial ischemia/infarction rates is responsible for the difference (28). Although, lipid-modifying medications have been demonstrated to attenuate all-cause and cardiovascular mortality in a retrospective study of a cohort of PD-treated patients (29), stronger evidence is required to establish the benefit of therapy. However, it is important to note that only 10% to 33% of PD patients are receiving statin therapy (30). Given the difference in atherogenic lipoprotein profile, it would seem inappropriate to apply the results of the 4D and AURORA trials, which recruited only HD-treated patients (who have normal or low levels of apoB) to the PD population (who have high levels of apoB). We are not aware of any group in which sustained high levels of apoB have not resulted in increased risk of cardiac death and in which statin therapy has not produced clinical benefit.

Where did the line of logic that stimulated the 4D and AURORA trials go wrong? Was the fact that apoB levels are not elevated in patients on HD the only weak link in the chain or is there yet another? We think there is, and we think it relates to the fact that the mechanisms of cardiac death in patients with ESRD need to be better illuminated. Until recently, almost all attention has been focused on just one—plaque rupture with acute thrombosis of an epicardial coronary artery. Reducing the incidence of plaque rupture is presumably the major mecha-

nism of the benefit of statins. However, other causes of sudden death, the leading mode of cardiac death in ESRD (1,31), need to be appreciated, understood, and remedied. These include factors that operate in all patients as well as those that may be more prominent in patients with severely impaired renal function. In the former category, there is plaque erosion that can also produce acute coronary thrombosis. In this case, the issue is a more gradual wearing away of the arterial endothelium consequent to inflammatory processes and altered glycoproteins within the arterial wall. Alternatively, platelet thrombi can form on altered endothelium and subsequently embolize to produce microinfarcts that can unleash fatal arrhythmias. Less commonly, the coronary lumen can be abruptly compromised because of hematoma in the subadvential space from a ruptured vasa vasorum or a coronary dissection. Statins will not be effective for any of these alternative mechanisms. Distinct from any of these discrete coronary events, sudden death has also been ascribed in dialysis patients to arrhythmia triggered by gross shifts of fluid and electrolytes in a setting of intermittent dialysis and a background of myocardial hypertrophy, coronary artery disease, and congestive heart failure (32). Multiple other mechanisms have been suggested, including abnormal microvascular perfusion and fibrosis, hyperphosphatemia, QT dispersion, sympathetic overactivity, autonomic nerve dysfunction, and angiotensin II-induced electric remodeling (33–35). Once again, statins would be expected to have little if any positive effect on these processes.

We would like to suggest yet another potential mechanism, one that has received little attention to date, but one that may be of substantial importance—reperfusion injury. Reperfusion injury occurs when severely ischemic myocytes are suddenly reperfused (36). This mechanism has been found to underlie much of the myocardial damage associated with cardiac surgery and after acute coronary reperfusion. We hypothesize this mechanism of myocardial injury may also be important in dialysis patients who frequently have fixed hemodynamically significant coronary artery lesions, hypertrophied left ventricles, and an underdeveloped capillary microcirculation. The combination creates a subendocardium with a capillary-cardiomyocyte mismatch that is vulnerable to recurrent ischemia. Add in anemia and the hypotension that so often accompanies intermittent dialysis and conditions for recurrent reperfusion injury seem robust. Perhaps this sequence is the origin of the elevated troponins that are so common in HD patients. Any particular event could be associated with a fatal arrhythmia, and a series of microinjuries or "infarctlets" to the left ventricle would result in progressive left ventricular dysfunction with heart failure and hypotension. Recent studies have demonstrated that a clinically silent but pronounced drop in myocardial blood flow frequently occurs during HD even in the absence of hemodynamically significant coronary artery disease or significant ultrafiltration (37,38). This sequence may well explain the regional cardiac wall motion abnormalities that occur frequently during HD and that are associated not only with significant reduction in left ventricular function over time, but a significant increase in the risk of death (39). Notably, patients with regional cardiac wall motion abnormalities had significantly higher interdialytic weight gains and predialysis cardiac troponin levels. Statins have been claimed to reduce experimental reperfusion injury, but whether they are effective in the clinical setting of uremia has not been demonstrated (40,41). To affect outcome in our patients on dialysis, controlled and observational studies examining the effects of a multipronged approach directed at attenuating activation of the sympathetic nervous system, the renin-angiotensin-aldosterone system, and mitigating volume and pressure overload are needed. Moreover, on the basis of the pathophysiological mechanisms we have outlined (32), efforts directed at more continuous forms of kidney replacement therapy may produce better short- and long-term outcomes for our patients (42).

Aurora, the Greek goddess of Dawn, was accused of being shortsighted by only asking Zeus for perpetual longevity but not eternal youth for one of her husbands. As a consequence, over time he grew steadily feebler and was ignored more and more until eventually he was relegated to obscurity (43). We believe that it would also be shortsighted of the nephrology community, on the basis of the AURORA trial, to consign all of the lipid abnormalities in all of the categories of patients with renal disease to obscurity.

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Dr. James Sloand is an employee of Baxter Corporation. Dr. Sniderman's wife, Dr. Sarah Prichard, is also an employee of Baxter Corporation. Dr. Sniderman has no personal financial relationships of any kind with Baxter Corporation. The other authors have no relevant conflicts of interest.

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