Response to ‘Treatment with statins may be considered in ESRD patients for primary prevention of cardiovascular disease’


Considering the clinical benefits of statins for primary and secondary cardiovascular event prevention in normal renal function patients, one can assume a similar benefit for patients with chronic kidney disease. Accordingly, Manca-di-Villahermosa’s letter reports that a small group of end-stage renal disease patients receiving atorvastatin show low cardiovascular mortality after 3 years of follow-up. However, in the 4-D study—the only randomized placebo-controlled statin trial done to date, which included 1255 patients with type 2 diabetes undergoing hemodialysis—atorvastatin administration was not associated with cardiovascular mortality reduction, which accounts for half the deaths in such patients. Moreover, this occurs independently of the presence or absence of high c-reactive protein levels that are associated with cardiovascular event risk. Reasons for this discrepancy are not evident, as statins exert anti-inflammatory, antioxidant, and lipid-lowering effects as effective as those observed in normal renal function participants. End-stage renal disease patients are at high risk for cardiovascular complications, in whom cardiovascular disease is considered complex and aggravated by coexisting factors, including malnutrition, accelerated atherosclerosis, left ventricular hypertrophy, cardiac fibrosis, and sympathetic overactivity. In the 4-D study, most of cardiovascular deaths were caused by sudden death and not by coronary heart disease. Data for two ongoing large trials (AURORA and SHARP) would help put into perspective statin’s beneficial effect in chronic kidney disease with respect to cardiovascular mortality. Apart from this, it has been reported that statin use is associated with sepsis incidence reduction—a major cause of moribundity in chronic kidney disease. This protective benefit could contribute to total mortality reduction in peritoneal dialysis and hemodialysis patients using statins reported by some observational studies (e.g., DOPPS).

Response to ‘On vascular calcification prevention with phosphonoformate and bisphosphonates’

Kidney International (2009) 75, 1356; doi:10.1038/ki.2009.113

Despite the fact that phosphonoformic acid (PFA) is a very weak inhibitor of the type III phosphate transporters present in vascular smooth muscle, its inhibition of calcification in cultured vascular smooth muscle cells (VSMCs) has been used to support a role for phosphate transport in vascular calcification.1 However, as pointed out by Villa-Bellosta and Sorribas,2 PFA is also a non-hydrolyzable analog of pyrophosphate (PPI). PPI is a potent, direct inhibitor of hydroxyapatite crystal formation that inhibits vascular calcification in vitro and in vivo, a property shared by a number of analogs, including bisphosphonates.3 Not surprisingly, Villa-Bellosta and Sorribas have shown that this is also the mechanism by which PFA inhibits calcification in VSMCs. This is yet another example of a ‘specific’ inhibitor that, like most ‘specific’ inhibitors, is not specific.

Subsequent studies using antisense RNA directed against Pit-1 have also shown inhibition of calcification in VSMCs,4 supporting a role for phosphate transport. However, caution must also be exercised in interpreting these results because VSMCs undergo substantial phenotypic changes in culture and lack the normal elastin matrix, which is the site of medial calcification in vivo. Using the whole aorta culture method, we have been unable to duplicate many of the findings in VSMCs related to medial calcification. Thus, the intriguing and potentially important role of phosphate transporters in vascular calcification, although widely cited, remains to be proven in a relevant model.


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