The Case against Calcium-Based Phosphate Binders

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Disturbances of mineral metabolism are associated with significant morbidity and mortality in patients with chronic kidney disease. Unfortunately, some of the treatments for these disturbances also have been found to be associated with morbidity. More recently, there is increasing evidence in the form of prospective, randomized trials that the use of calcium-based phosphate binders contributes to progressive coronary artery and aorta calcification compared with the non–calcium-containing binder sevelamer. Moreover, there is compelling biologic plausibility that hyperphosphatemia and excess exogenous calcium administration can accelerate vascular calcification. Unfortunately, there is no bedside test that can determine whether there is a dose of calcium salts (either as maintenance or as cumulative dose) that can be administered safely, and, unfortunately, the serum calcium concentration does not reflect calcium balance. Therefore, calcium-based phosphate binders should be avoided in many, if not most, patients who are undergoing dialysis.

Our patients can be thankful that nephrology has advanced over the years. We have moved beyond the Scribner shunt and the Kiil dialyzer and developed new and improved dialytic therapies. We have new drugs to treat anemia and have recognized that the progression of chronic kidney disease (CKD) can be slowed. Fortunately, we also have gained considerable insight into disorders of mineral metabolism, which has led to a new treatment paradigm. Herein we review these historical gains.

Secondary hyperparathyroidism has been a known complication of advanced CKD for some time. In the 1970s and 1980s, conventional wisdom surrounding the pathogenesis of secondary and tertiary hyperparathyroidism was that calcium was the only regulator of parathyroid hormone (PTH) secretion, and PTH was a primary uremic toxin. Control of phosphorus with aluminum-based binders was believed to be important to avoid a high calcium × phosphorus product so that calcium levels could be pushed to supraphysiologic levels to fulfill the primary objective, which was PTH suppression. It was taught that patients with advanced hyperparathyroidism had an altered set point, or sensitivity of the glands to calcium, and therefore required supraphysiologic levels of calcium to suppress PTH. Supplementation with vitamin D was used to enhance gastrointestinal absorption of calcium and indirectly raise serum calcium concentrations (1). When the toxicity of aluminum overload became apparent (2), calcium salts were heralded as the best possible alternative phosphate binder because it could control serum phosphorus and it had the added "advantage" of raising serum calcium levels to suppress PTH (3). In essence, the global dialysis community embraced the concept that calcium was *the* treatment to avoid all evils of secondary hyperparathyroidism. There was no recognition of the direct toxicity of phosphorus and calcium on extraskeletal tissues.

Our scientific understanding continued to advance. In the late 1980s and early 1990s, there was recognition that activated vitamin D [1,25(OH)$_2$D, or calcitriol] not only increased intestinal calcium absorption but also *directly* suppressed PTH secretion (4,5). We then embraced the use of large doses of calcitriol to suppress PTH, gradually raising the "acceptable" calcium × phosphorus product to the 75-mg^2/dl^2 range despite the absence of data supporting the safety of this strategy. However, even with a broad calcium × phosphorus product tolerance range, treatment with moderate- to high-dose calcitriol often led to hypercalcemia and hyperphosphatemia. As a result, second-generation vitamin D analogues were developed with more activity at the parathyroid gland and less activity at the intestine to maximize suppression of PTH secretion (6). Research advances also demonstrated that phosphorus directly increased PTH secretion (7). The treatment paradigm of the 1990s was to control phosphorus and give calcium and calcitriol to achieve the primary objective of PTH suppression. There still was little recognition of the direct toxicity of phosphorus and calcium independent of PTH on extraskeletal tissues.

In 1998, the landmark paper of Block *et al.* (8), which used data from two established cohorts from the United States Renal Data System, was published. In this report, the authors demonstrated that hyperphosphatemia and high calcium × phosphorus product were independently associated with increased mortality in hemodialysis patients. This study confirmed an observation made by Lowrie and Lew in 1980 (9). The earlier study also identified hypoalbuminemia as a potent predictor of mortality, and that association was so monumental that the relation between hyperphosphatemia and mortality received limited attention. The Block *et al.* study (8) was criticized with the argument that hyperphosphatemia was principally a sur-

rogate for noncompliance. However, in the past several years, the association of hyperphosphatemia with mortality has been confirmed in a large cohort from Fresenius (10), the international Dialysis Outcomes and Practice Patterns (DOPPS) study (11), a Netherlands cohort (12), and a more contemporary United States Renal Data System cohort (13). Therefore, observational data have clearly documented an association of hyperphosphatemia and mortality throughout the world. In all of these studies, the primary cause of death was cardiovascular disease. *In vitro* studies also have demonstrated that phosphorus, at concentrations that commonly are observed in patients with ESRD, induces phenotypic transformation of vascular smooth muscle cells into cells that resemble osteoblasts, resulting in vascular calcification (14). Studies in patients with CKD further demonstrated that hyperphosphatemia was associated with hypertension, hyperkinetic circulation, increased cardiac work, high arterial tensile stress (15), and, more recently, diastolic dysfunction (16). These and other studies that followed provided biologic plausibility for an association of hyperphosphatemia with mortality and cardiovascular disease.

Critical Point 1: Phosphorus is a uremic toxin.

The data supporting an association between hypercalcemia and mortality is less robust. Some studies have failed to find an association (8), whereas other, more recent studies that more thoroughly controlled for confounders have demonstrated that hypercalcemia is associated with increased mortality (10,11). One study reported the risk attributable to various factors, taking into account the strength of the association (*i.e.*, relative risk) and prevalence across the population (10). The results (Figure 1) demonstrate that hyperphosphatemia conveyed a very high population-attributable risk for death (even more than anemia and a low urea reduction ratio [URR]) and that the combination of hyperphosphatemia, hypercalcemia, and elevated PTH accounted for 17.5% of the observed, explainable mortality risk in patients with ESRD. Advocates of calcium-based binders stop here and argue that calcium-based binders therefore are toxic only in the setting of hypercalcemia, but the nephrologist (and endocrinologist and the physiologist) who understands the difference between homeostasis and balance knows that there is more to calcium than meets the eye on the laboratory report. For years we have taught that serum sodium concentrations do not reflect total body sodium in evaluating the dysnatremias. However, the concept that serum calcium levels do not reflect total body calcium remains foreign to some, especially those who advocate pharmacologic doses of calcium salts for use as phosphate binders. We briefly explain this concept while also referring the reader to excellent reviews on the subject (17,18).

Balance is the net intake minus the net excretion of any substance. In neutral balance, the intake equals the output. In the case of calcium, nature (or one's preferred higher power) has devised a system that keeps the body in positive calcium balance (more in than out) when bones are growing to increase linear growth. After peak bone calcium content is achieved at approximately age 25 to 30, nature favors neutral calcium balance whereby calcium intake is excreted *via* stool and urine. In
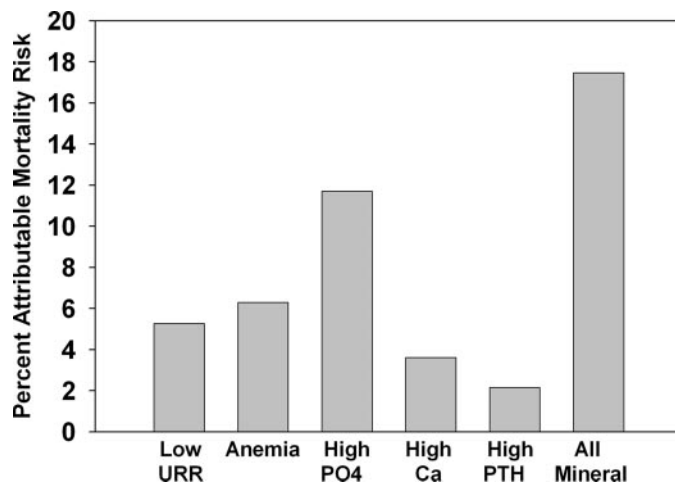

Figure 1. Attributable risk for disorders of mineral metabolism. The population-attributable risk for mortality in a large (39,530) cohort of hemodialysis patients for several laboratory abnormalities was determined (10). Several variables were considered: Hyperphosphatemia (high PO_4, defined as serum phosphorus ≥5.0 mg/dl), hypercalcemia (high Ca, defined as serum calcium ≥10 mg/dl), and moderate to severe hyperparathyroidism (high parathyroid hormone [PTH], defined as PTH ≥600 pg/ml) individually and in combination. We compared these with population-attributable risk percentages for inefficient dialysis (low urea reduction ratio [URR], defined as URR <65%) and anemia (defined as hemoglobin <11 g/dl). The attributable risk associated with disorders of mineral metabolism (17.5%) was higher than that associated with inefficient dialysis (5.1%) or anemia (11.3%).

postmenopausal women, estrogen deficiency decreases intestinal calcium absorption, creating negative calcium balance that then is neutralized (not made positive!) with calcium supplements. However, it should be pointed out that calcium should be viewed as an adjunct therapy (as opposed to primary therapy) for fracture prevention in postmenopausal osteoporosis. A recent study in >36,000 postmenopausal women found the daily intake of 1000 mg of elemental calcium and 400 IU of vitamin D_3 led to small, significant changes in bone mineral density but did not decrease the risk for hip fractures (19). The rationale for calcium in the treatment of postmenopausal osteoporosis is to provide adequate stores while net bone formation (or decreased bone resorption) is facilitated with the use of bisphosphonates and other antiosteoporotic agents. In reality, calcium supplements would be much more effective if provided to children and adolescents when bone is growing to achieve a greater peak bone mass rather than to the middle-aged and elderly, in whom bone does not anabolize.

Nature facilitates calcium into growing bones, discarding the rest in the urine through the actions of PTH. Therefore, when normal calcium-PTH homeostasis is altered by CKD as a result of concomitant abnormalities of phosphorus clearance, vitamin D metabolism, and decreased GFR, there is a disconnection between calcium homeostasis and calcium balance. This situation is similar to other dysregulated homeostasis-balance pathways in the setting of CKD. For example, potassium homeosta-

sis is regulated primarily by aldosterone *via* excretion by the kidneys. When kidney function is impaired, potassium balance becomes net positive. Nephrologists therefore step in as a "surrogate homeostasis pathway" to ensure normal potassium balance by prescribing decreased intake and to ensure enhanced clearance *via* loop diuretics or cathartics or, at end stage, with dialysis. The same level of oversight should occur for calcium. In the setting of altered homeostasis in patients with CKD, the nephrologist needs to take an active role in ensuring neutral calcium balance by decreasing intake and by enhancing the capacity of bone to take up calcium (20). The latter can be accomplished by avoiding oversuppression of PTH; this in turn is accomplished by avoiding injudicious use of calcium and vitamin D. Unfortunately, only 0.1% of total body calcium is in the extracellular space; therefore, nephrologists cannot determine calcium balance or total body calcium content by measuring serum calcium levels or assess whether the calcium intake (or "load") is sufficient, insufficient, or excessive by measuring serum calcium levels. Unfortunately, no simple laboratory test currently exists to assess calcium balance.

Critical Point 2: Serum calcium levels do not reflect calcium balance.

Given the lack of laboratory tests to determine calcium balance, one must use best judgment to determine the needed calcium intake to maintain neutral balance. In CKD stages 3 and 4, patients may require either calcitriol or low-dose calcium supplements to maintain neutral balance. This is because of impaired gastrointestinal absorption of calcium with decreased calcitriol levels and continued urinary calcium excretion and bone uptake. At the other extreme, a dialysis patient who is anuric loses calcium only in stool and sweat, as there is very little net exchange of calcium with dialysis (21). On average, the Institute of Medicine estimates that the daily loss of calcium in stool and sweat may be approximately 200 mg/d. The net absorption of calcium from the gastrointestinal track is between 15 and 30% (it is higher on calcitriol). Therefore, if we assume that there is no uptake of calcium into bone or any significant flux from the dialysate, then the patient would need 800 mg/d (200 mg if 25% intestinal absorption) of elemental calcium intake to maintain neutral balance. This easily can be in the form of diet, although as a result of phosphorus restriction, many dialysis patients consume closer to 400 to 500 mg/d calcium. Therefore, depending on the diet, an additional intake of up to 300 mg/d elemental calcium *may* be needed. This is approximately the absorption from two calcium carbonate tablets (1000 mg of elemental calcium × 30% absorption) and six calcium acetate tablets (1002 mg of elemental calcium intake × 30% absorption). However, this calculation is based on many assumptions, which is the primary reason that the Kidney Disease Outcomes Quality Initiative guidelines provide only a maximum daily intake and not a needed daily intake (22). In the end, we really do not know whether patients require any calcium supplements if they are eating an adequate diet, especially in light of new data in postmenopausal women showing that calcium does not have the positive bone effects that we have believed for years (19).

The Case against Calcium Binders

Patients with CKD have been plagued with extraskeletal calcification for years, so the phenomenon indeed is not new. What has changed, however, is an increased understanding of the mechanism of vascular calcification and the ability to quantify vascular calcification with computed tomography (CT), including electron-beam CT and, more recently, helical CT. As we have highlighted, new knowledge leads to innovative treatment paradigms.

In the past, vascular calcification was believed to be due to necrotic tissue with secondary calcification of the atherosclerotic plaque (23). More recently, advances in noninvasive imaging with pathologic correlates have identified concentric calcification of the intima to occur early in the course of atherosclerotic disease (24). In addition, clinical studies in patients with diabetes identified medial calcification of the distal arteries, formerly thought to be of minimal consequence, associated with increased mortality (25). Recent advances also have increased our understanding of the pluripotential capability of stem cells. This capability often is retained in differentiated cells, with a phenotype maintained by turning on or off certain transcription factors. In the 1990s, important work by several investigators found evidence for a phenotypic switch of vascular smooth muscle cells to bone-like cells in both atherosclerotic and medial calcification (26–28). Multiple studies have identified several factors that may induce such a phenotype change, including elevated phosphorus concentrations, fluid sheer stress (as induced by hypertension and large intradialytic weight gain), altered cytokines, diabetes, and hyperglycemia (reviewed in reference [29]). Subsequent work demonstrated that these transformed, osteoblast-like vascular smooth muscle cells are capable of mineralizing *in vitro* in the presence of high phosphorus, with additive effects of high calcium (30,31).

How does mineralization occur in arteries? The precise mechanism is not understood, but it seems to parallel the process in bone whereby the bone-forming cell (osteoblast) lays down a matrix, or scaffolding, of collagen and noncollagenous proteins. Then, in the presence of enough phosphorus and calcium, mineralization occurs, with the process regulated by proteins that inhibit mineralization. These data suggest that vascular smooth muscle cells in uremia that have been exposed to hyperphosphatemia, hypertension, or hyperglycemia (to name a few toxins) behave like osteoblasts and deposit collagen and noncollagenous proteins in the arterial wall. Then, in the presence of hypercalcemia, hyperphosphatemia, and excess calcium load, the vessel mineralizes. Supporting this sequential process in CKD, Moe and colleagues (32) found evidence for deposition of this matrix even before overt calcification in inferior epigastric arteries of patients who had ESRD and underwent a kidney transplant. It is no wonder that vascular calcification has been around for years. These stressors and the ability of cells to change phenotype likely have been around for years. Advocates of calcium-based phosphate binders argue that vascular calcification is not new and, therefore, that calcium binders cannot be implicated. We would argue that what really has happened over the last 30 yr is a change in the cause of excess calcium load, from severe secondary hyperparathyroidism

(with excess release of calcium from bone) to high-dose vitamin D (with increased intestinal absorption and decreased bone turnover) to high-dose calcium binders. In essence, the arteries of our patients are primed to become calcified from a lot of stressors; the process then is accelerated with excess calcium load in the form of binders. This is worsened further by high-dose vitamin D and low levels of physical activity, which further enhance intestinal calcium absorption and impair bone turnover.

Critical Point 3: Vascular calcification is not merely a passive process but a cell-mediated process accelerated by hyperphosphatemia and excess calcium load.

Advances in noninvasive imaging have led to increased recognition of the importance of arterial calcification. Calcified arteries cause decreased arterial compliance (33,34), which can be assessed by increased pulse wave velocity and increased pulse pressure, both of which are associated with increased mortality in patients with ESRD (34,35). Goodman *et al.* (36) found that coronary artery calcification as assessed by electron-beam CT was markedly increased in adolescents and young adults and that the amount of calcium binder prescribed was associated with increased calcification. Similarly, Guerin *et al.* (34) found that the magnitude of large artery calcification was associated with increased intake of calcium binders. It is true that not all studies have found such an association as reviewed by McCullogh *et al.* (37). Therefore, there is a need for a prospective, randomized trial.

The Treat to Goal study was the first such prospective, randomized trial to test the hypothesis that non–calcium-containing phosphate binders attenuate arterial calcification. Of note, this also is the first study to evaluate the role of a phosphate binder on *any* end point other than control of phosphorus and/or PTH levels. The Treat to Goal study randomly assigned 200 dialysis patients across the United States to either calcium acetate or calcium carbonate (United States or Europe, respectively) or the non–calcium-containing binder sevelamer. The study was called Treat to Goal because the target end points were very aggressive (especially when one considers that they predated the Kidney Disease Outcomes Quality Initiative). After the first 12 wk, when the binder was adjusted in an effort to maintain serum phosphorus in the 3.0- to 5.0-mg/dl range, vitamin D could be adjusted to maintain intact PTH at target levels of 150 to 300 pg/ml. Patients were treated for up to 52 wk. The results demonstrated that coronary artery and aorta calcification increased in the calcium binder arm, whereas there was no significant change in the sevelamer arm over 1 yr (38) (Figure 2). A 1-yr (total 2-yr) extension study of patients in Europe confirmed longer term benefits (39). Of importance, this increased calcification in the calcium binder arm occurred despite equivalent serum calcium, phosphorus, and calcium × phosphorus product in both arms (although there were more hypercalcemic episodes in the calcium arm). These results clearly demonstrated that calcium-based binders increase vascular calcification and/or that the non–calcium-based binder sevelamer halts the natural progression of vascular calcification. It is not known whether other non–calcium-based binders
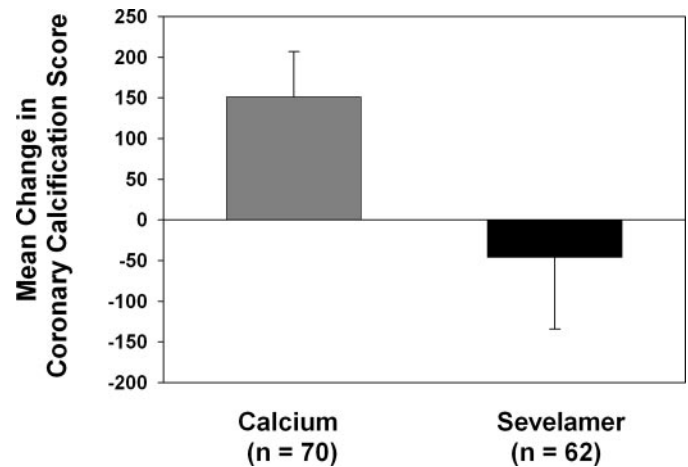

Figure 2. Change in coronary artery calcification in patients who were treated with calcium or sevelamer. In a prospective, randomized study, the non–calcium-based phosphate binder sevelamer (■) was compared with calcium-based phosphate binders (▧). The primary end point was change in coronary artery calcification, shown as the mean percentage change. Patients who were treated with calcium-based phosphate binders had an increase in coronary artery calcification. In contrast, patients who were treated with sevelamer had no increase in coronary artery calcification ($P < 0.05$ compared with baseline in calcium group, and compared with other group). Adapted from reference (38), with permission.

such as lanthanum carbonate have similar effects, because no similar studies have been conducted.

Of course, there always are critics of every study. Critics of the Treat to Goal study argued the following: (*1*) The sevelamer patients took calcium supplements, negating the role of calcium binder, but in reality, only 15 patients in the sevelamer arm and five patients in the calcium arm took evening calcium supplements (data on file, Genzyme). (*2*) The study did not control for vitamin D use. It would have been unethical not to control PTH in a year-long study. Furthermore, the sevelamer arm received significantly more vitamin D, negating this argument. (*3*) The study was not placebo controlled. This would have been difficult because of the differences in pill shape and size, and it would have led to twice as many pills per patient, having a negative impact on compliance. Furthermore, the end points were objective measurements and therefore unlikely to have been affected by any "placebo" type effect. (*4*) The benefit from sevelamer was due to the lipid-lowering effect of sevelamer. This may have played a role, but there was no correlation with LDL and vascular calcification at baseline (38) and no association between baseline or change in lipid levels and the change in calcification (40). In addition, statins, with equivalent LDL lowering, failed to reduce mortality in a large clinical trial of hemodialysis patients with type 2 diabetes (41), and a recent randomized trial demonstrated that statins do not ameliorate coronary artery calcification in the general population (42).

Supporting the Treat to Goal study is a recently published study that compared calcium-based phosphate binders to sevelamer in patients who were new to dialysis. The results

also showed progression of coronary artery calcification in the calcium-treated arm and no progression in the sevelamer arm (43). Therefore, the only two human, prospective, randomized trials to evaluate vascular calcification as an end point have demonstrated that sevelamer attenuates vascular calcification, whereas calcium binders led to progression. Of importance, this was in the setting of identical phosphorus control, dispelling the myth that it is "phosphification" and not calcification as the proponents of calcium acetate suggest. Furthermore, animal studies have confirmed these findings (44,45). Although the Treat to Goal study was not designed to identify the mechanism(s) by which calcium binders increased arterial calcification, the difference in calcification is almost certainly due, in part, to calcium load, which may directly enhance vascular calcification and may indirectly accelerate this process by reducing bone remodeling, rendering the bone incapable of taking up any calcium. The latter is supported by the finding that PTH was more often oversuppressed in the calcium arm and that CT-based attenuation (calcium content of cancellous bone) was decreased in the calcium binder arm and increased in the sevelamer arm in a secondary analysis (46) (Figure 3). Simply put, in patients treated with calcium-containing phosphate binders, calcium deposited in the arteries instead of the bone. **Critical Point 4: In prospective, randomized studies, calcium-based phosphate binders led to increased arterial calcification, whereas the non–calcium-based phosphate binder sevelamer did not.**
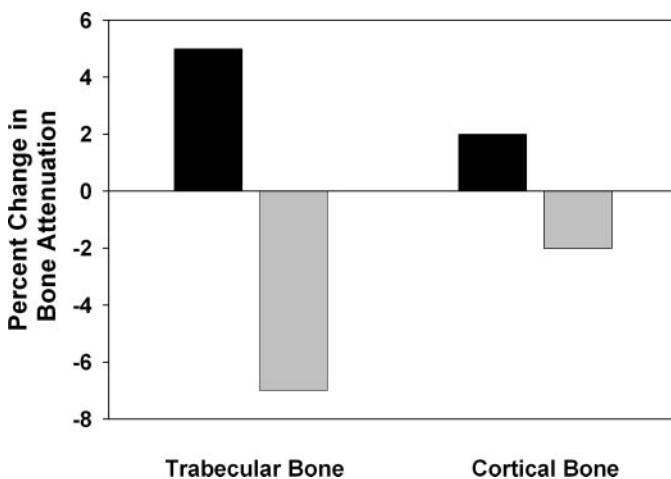
Critics of these studies (and proponents of calcium-based binders) argue that arterial calcification has not been shown to be associated with mortality in patients with ESRD. Two studies in patients with ESRD have shown increased mortality with increasing coronary artery calcification by CT imaging (47,48), and another larger, unpublished study (Block *et al.*, personal communication). Furthermore, large artery calcification (either intimal or medial) has been shown to predict mortality in patients with ESRD (49). Even stronger data exist in the general population, in whom coronary artery calcification is predictive of future cardiac events in studies of asymptomatic and symptomatic individuals without CKD (50–52).

Conclusion

There is clear evidence in the form of prospective, randomized trials that calcium-based binders are associated with increasing arterial calcification compared with the non–calcium-based phosphate binder sevelamer. There is sound biologic plausibility as to the mechanism by which excess calcium load from binders contributes to vascular calcification. As nephrologists, we should leave the old treatment paradigms behind us and advance our patient care into the 21st century as supported by advancements in science.

Figure 3. Change in bone in patients who were treated with calcium or sevelamer. In a secondary analysis of the thoracic spine from the Treat to Goal study, the attenuation, which is a measure of calcium content, was assessed in paired (pre-post) electron-beam computed tomography scans. Compared with sevelamer-treated patients (■), calcium-treated patients (▦) showed a decrease in thoracic vertebral trabecular (cancellous) bone attenuation ($P = 0.01$) and a trend toward decreased cortical bone attenuation. More than 30% of calcium-treated patients experienced a 10% or more decrease in trabecular (cancellous) and cortical bone attenuation. Reprinted from reference (46), with permission.

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