Pro: Cardiovascular calcifications are clinically relevant

Jordi Bover 1, Pieter Evenepoel 2, Pablo Ureña-Torres 3,4, Marc G. Vervloet 5, Vincent Brandenburg 6, Sandro Mazzaferr 7, Adrian Covic 8, David Goldsmith 9, Ziad A. Massy 10,11 and Mario Cozzolino 12

on behalf of the CKD-MBD Working Group of ERA-EDTA

1 Fundació Puigvert, Department of Nephrology, IIB Sant Pau, RedinRen, Barcelona, Catalonia, Spain, 2 Department of Nephrology and Renal Transplantation, University Hospitals, Leuven, Belgium, 3 Department of Nephrology and Dialysis, Clinique du Landy, Saint-Ouen, France, 4 Department of Renal Physiology, Necker Hospital, University of Paris Descartes, Paris, France, 5 Department of Nephrology and Institute for Cardiovascular Research VU (ICaR-VU), VU University Medical Center, Amsterdam, The Netherlands, 6 Department of Cardiology and Intensive Care Medicine, RWTH University Hospital Aachen, Aachen, Germany, 7 Department of Cardiovascular, Respiratory, Nephrologic and Geriatric Sciences, Sapienza University of Rome, Rome, Italy, 8 Clinic of Nephrology, C.I. Parhon University Hospital, Gr. T. Popa, University of Medicine and Pharmacy, Iasi, Romania, 9 King’s Health Partners AHSC London, London, UK, 10 Division of Nephrology, Ambroise Paré Hospital, Paris Ile de France Ouest University, Paris, France, 11 INSERM U1088, Picardie University Jules Verne, Amiens, France and 12 Department of Health Sciences, Renal Division and Laboratory of Experimental Nephrology, San Paolo Hospital, University of Milan, Milan, Italy

Correspondence and offprint requests to: Mario Cozzolino; E-mail: mario.cozzolino@unimi.it

ABSTRACT

It is increasingly acknowledged that mineral and bone disorders (MBDs) contribute to the excessively high cardiovascular (CV) disease morbidity and mortality observed in patients with chronic kidney disease (CKD). There is ongoing debate as to whether screening for CV calcification, one of the hallmarks of CKD-MBD, should be implemented in clinical practice in patients with CKD. Issues to be considered in this controversy relate to prevalence, severity, relevance, and last but not least, modifiability and reversibility of vascular and valvular calcifications in the setting of CKD. The recent expansion of the armamentarium to treat CKD-MBD (calcium-free phosphate binders and calcimimetics) creates new opportunities. Mounting experimental and clinical evidence indicates that progression of CV calcification may indeed be attenuated. Whether this will translate into better outcomes remains to be proven. We acknowledge that hard outcome data so far are limited and, overall, yielded inconclusive results. Nevertheless, in an era in which personalized medicine has gained much popularity, we consider it reasonable, awaiting the results of additional studies, to screen for CV calcification in selected individuals. This policy may help to stratify CV risk and to guide therapy. We speculate that such an approach will ultimately improve outcomes and reduce health costs.

Keywords: chronic kidney disease, dialysis, hyperphosphataemia, vascular calcification

INTRODUCTION

Chronic kidney disease (CKD) is an independent cardiovascular (CV) risk factor and the risk of death increases exponentially with the progressive decline of renal function. Traditional and non-traditional CV risk factors, including disorders of mineral and bone metabolism, are suggested to account for the extreme CV morbidity and mortality rates in CKD patients. In 2006, the term CKD-mineral and bone disorder (CKD-MBD) was coined to describe a syndrome that is manifested by abnormalities in mineral and bone metabolism and/or extra-skeletal calcifications [1, 2]. Intense cross talk exists between the bone and the vasculature, which is commonly referred to as the bone-vascular axis, and the pathological hallmarks of parallel diseased bone and arterial vessels...
are renal osteodystrophy and vascular calcification (VC), respectively. However, there is an ongoing debate on the clinical relevance of VC and the need to screen for this condition in CKD. Important issues to account for in this controversy relate to prevalence, clinical significance, ability to prevent and reversibility of the condition. The key question is whether screening of VC will ultimately translate into better outcomes. In the next sections, we will provide sound evidence that CV calcification is highly prevalent and rapidly progressive in CKD, that it is directly and possibly causally related to poor hard outcomes and that it is modifiable. Acknowledging the many gaps in the evidence, we conclude that in an era in which personalized medicine is emerging as an important approach, evaluation of CV calcification may be defended, at least in selected cases.

VASCULAR AND VALVULAR CALCIFICATIONS ARE MORE PREVALENT AND RAPIDLY PROGRESSIVE IN CKD: CLINICAL AND EPIDEMIOLOGICAL DATA

Four types of CV calcifications have been described in uraemia: (i) classical calcified atherosclerotic plaque; (ii) arterial media calcification, medial calcinosis or Monckeberg’s disease; (iii) cardiac valvular calcifications and (iv) calciphylaxis or calcific uraemic arteriolopathy. The latter condition, although conferring an extreme mortality risk, is very rare and beyond the scope of the present discussion.

CV calcification is neither a new phenomenon nor is it exclusive of CKD as it is highly prevalent in diabetes and ageing. However, both prevalence and severity are remarkably high among CKD patients [1, 2], even in early stage disease and among children and adolescents. Reported prevalence rates show an important variation (i.e. 47–93%) [1], related to both case-mix, differences in sensitivity of diagnostic methods applied and differences in arterial territories assessed [3–5]. So far, no study has systematically evaluated the distribution of CV calcifications at different sites in large CKD populations across stages of disease. Overall, when CV calcifications are detected in uraemic subjects, they are usually more prominent in the thoracic and abdominal aorta than in the coronary arteries [3]. Moreover, once CV calcifications are established in the setting of CKD, they follow a more rapidly progressive course than in non-CKD subjects [calcium (Ca) begets Ca] [1, 5]. This accelerated course of CV calcifications is probably related to the accelerated atherosclerosis or ageing-senescence processes that affect these patients, probably because CKD-related factors act as powerful catalysts. In contrast, CKD patients without CV calcifications seem to have a high likelihood of remaining free of VC over months to years, possibly reflecting an unidentified defence mechanism.

There is comprehensive experimental evidence relating mineral disorders as inducers and promoters of CV calcification, mainly related to the direct and indirect vascular toxicity of phosphate (P) and Ca beyond their passive precipitation on the vessel wall [6, 7]. The cellular osteochondrocytic transdifferentiation of mesenchymal stem cells or vascular smooth muscle cells (VSMCs) into osteoblast-like cells is well documented, especially in uraemic conditions [7, 8]. However, this phenomenon may differ among arterial regions since no evidence for osteogenic transdifferentiation or apoptosis of VSMC has been observed in calcified breast arteries from uraemic women [9]. Moreover, as a highly organized and tightly regulated process, systemic or local inhibitory factors of CV calcification are overwhelmed in CKD patients by a multitude of promoters that induce VSMC damage and cell death, resulting in an undesirable imbalance favouring excessive CV calcification. This bewildering issue is beyond the scope of this manuscript and we refer readers to comprehensive recently published reviews [7, 8, 10].

VASCULAR AND VALVULAR CALCIFICATIONS INDEPENDENTLY ASSOCIATE WITH DISMAL OUTCOMES

Once mainly considered a dystrophic lesion related to ageing, CV calcification is currently recognized as a significant cause of morbidity and mortality both in the general population and in all CKD patients, from early stage disease through dialysis to renal transplantation [1, 5]. Several clinical studies have shown that any form of CV calcification represents a marker of systemic vascular disease and is associated with unfavourable outcomes [5]. In populations at high risk for CV disease such as diabetics, evaluation of coronary artery calcification (CAC) is an accepted tool for CV risk assessment (level of evidence B) [11]. Moreover, progression of CV calcification provides independent incremental prognostic information, and it is associated with worsening of other markers of vasculopathy and myocardio-pathy [5]. More importantly, it has been recently shown that the CAC score significantly improved the CV risk prediction model beyond traditional CV risk factors in subjects with CKD [12].

Intimal calcification of atherosclerotic plaques is clearly associated with CV events. The previously held notion that calcification is a late phenomenon and stabilizes atherosclerotic plaques is currently strongly disputed [13, 14]. Medial calcification, as an expression of arteriosclerosis, induces arterial stiffness and increases pulse-wave velocity, contributing to left ventricular hypertrophy and heart failure. Aortic valve calcification is associated with valvular stenosis that may lead to left ventricular remodelling, hypertrophy and dysfunction. Mitral valve calcification may result in mitral insufficiency or stenosis, conditions that have been associated with cardiac arrhythmias, infectious endocarditis, thromboembolic events, cardiac insufficiency and stroke. Of note, most CKD patients have these three types of CV calcification simultaneously (Figure 1) [8].

CV CALCIFICATION IS A MODIFIABLE RISK FACTOR: FROM EXPERIMENTAL TO CLINICAL STUDIES

Given its central role in the pathogenesis of CV calcifications, a disordered mineral and bone metabolism is and has been a major therapeutic target in many animal and clinical intervention studies [6, 15–21]. The armamentarium to combat
CKD-MBD has expanded substantially in recent years, e.g. with the introduction of Ca-free P binders, calcimimetics or new vitamin D analogues. This creates new opportunities, but meanwhile complicates therapeutic decision-making.

**Targeting phosphate**

A disordered P metabolism is an early complication of CKD (Table 1). It is well established that an abnormal P metabolism is not only a major contributor to VC, as shown in many preclinical models, but it is also associated with poor CV clinical outcomes [1, 6, 7, 14, 15]. Besides dietary P restriction, P binders are the mainstay in the treatment of hyperphosphataemia. Since the introduction of sevelamer, evidence has accumulated that this non-Ca-based P binder attenuates the progression of CV calcification when compared with Ca-based P binders [1, 17, 18, 21]. Consequently, the 2009 KDIGO guideline suggested to restrict the dose of Ca-based P binders in the presence of VC ‘at least until more definitive studies are conducted’ [1]. It should be emphasized that this recommendation was formulated against the background of a negative hard outcome trial with sevelamer (Dialysis Clinical Outcomes Revisited—DCOR trial) [22]. This recommendation also deviated from the 2003 American NKF-K/DOQI guidelines to restrict Ca-based P binders in patients presenting with severe VC only (a situation where it may be even too late to modify its consequences).

In recent years, several studies have reinforced the thesis that non-Ca-based P binders, including sevelamer, lanthanum carbonate and possibly also magnesium-based P binders, attenuate the progression of VC when compared with Ca-based P binders [23, 24]. Furthermore, a survival benefit was demonstrated for non-Ca-based P binders in randomized clinical trials (RCTs; both in CKD 3–4 and CKD 5D populations) [25, 26] and in a recent meta-analysis [27]. Nonetheless, these studies did not address whether non-Ca-based P binders are inherently beneficial or whether Ca-based P binders are harmful. A recent randomized placebo-controlled study in normophosphataemic CKD patients stages 3B–4 (n = 148, eGFR = 20–45 mL/min/1.73 m², mean serum P 4.2 mg/dL) of three different P binders (Ca acetate, sevelamer carbonate and lanthanum carbonate) revealed an unexpected increase in CV calcification in CKD patients on active treatment. This increase was most pronounced in the Ca

**FIGURE 1:** (A) Aortic valve with massive macroscopically detectable calcification, explanted due to calcific aortic stenosis, from a dialysis patient. (B) Transversal, sagittal and lateral views of arterial calcifications from a dialysis patient.
In summary, recent evidence emphasizes concerns with regard to liberal use of Ca-based P binders with regard to progression of CV calcifications in patients with established VC. This evidence was recently considered strong enough by the KDIGO workgroup to advise revision of the current guidelines. Evidence regarding primary prevention of VC via Ca restriction is much less substantiated.

### Targeting parathyroid hormone

Calcimimetics potently suppress parathyroid hormone (PTH) and reduce circulating concentration of Ca × P product, and thereby represent an attractive alternative for active vitamin D sterols as treatment for secondary hyperparathyroidism (Table 1). In addition to unequivocal experimental data showing a neutral or protective effect of calcimimetics on uremia-enhanced CV calcification [16, 30], cinacalcet added to fixed low-dose vitamin D sterols tended ($p = 0.07$) to attenuate CV calcification in haemodialysis patients when compared with standard therapy [3], and this effect was statistically significant in protocol-adherent patients [20]. The EVOLVE study [31] comparing calcimimetics versus standard therapy in 3883 haemodialysis patients with moderate-to-severe secondary hyperparathyroidism failed to show a significant reduction of mortality or major CV events in cinacalcet-treated patients in an unadjusted intention-to-treat analysis. Likewise, a recent meta-analysis showed that calcimimetics do not improve all-cause or CV mortality [32]. Accordingly, as it happened with sevelamer and the DCOR study [22], a direct link between therapeutic strategies that potentially attenuate the progression of VC in dialysis patients and survival benefits could not be definitely established. However, it is important to emphasize that, in addition to other patient-level nominally significant beneficial effects associated with sevelamer and cinacalcet use [22, 31], a statistically significant age interaction on the treatment effect was observed in both RCTs. For instance, both drugs decreased the mortality rate in a predefined cut-off of patients over 65 years of age, probably due to a higher statistical power related to a higher number of CV events occurring in this age group. A similar interaction has also been observed with lanthanum carbonate. In the case of the EVOLVE study, cinacalcet significantly reduced the risk of death or major CV events in a secondary predefined adjusted intention-to-treat analysis [31].

### Calcidiol and vitamin D receptor activators

Low calcidiol levels represent a novel CV risk marker and have been directly associated with the presence and progression of VC (Table 1) [33]. Consequently, maintaining normal levels seems to be desirable to reduce the progression of VC and to maintain normal bone turnover [33], apart from other described vitamin D pleiotropic effects [8]. Experimental studies have shown differential effects of calcitriol or other vitamin D receptor activators (VDRAs) on VC, the former being a classic dose-dependent inductor of experimental VC [16]. On the other hand, lower doses of both calcitriol and paricalcitol seemed to be protective probably through restoration of klotho and osteopontin expression [34]. Thus, a U-shaped dose response of VDRAs can be postulated with regard to VC. In general, the experimental data supporting less toxicity of some VDRAs, compared with calcitriol, are not consistent across studies, but they seem to support the claim that there is reduced induction of VC with different VDRAs such as paricalcitol [15]. A consistent survival benefit of VDRA treatment in haemodialysis patients has been described only in several retrospective studies and a recent meta-analysis [35, 36], and although it has been questioned, the benefit seemed to be more pronounced in the low-dose range and among patients who received a vitamin D analogue [35]. It should be emphasized that, at present, no prospective RCT confirmed these results, leaving an important gap in the evidence.

### Other potential future treatments

Since vitamin K deficiency is common in ESRD, and antagonizing vitamin K (e.g. warfarin) may promote VC through upregulation of uncarboxylated matrix Gla protein and osteocalcin, several prospective RCTs are currently evaluating the

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**Table 1. Comparison of distinct effects of P binders and anti-parathyroid agents on CKD-MBD laboratory parameters, progression of VC and/or survival**

<table>
<thead>
<tr>
<th>P binders</th>
<th>Ca</th>
<th>P</th>
<th>Ca × P</th>
<th>PTH</th>
<th>VC</th>
<th>Survival</th>
</tr>
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<tbody>
<tr>
<td>Aluminium</td>
<td>–</td>
<td>↓↓</td>
<td>↓</td>
<td>–</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ca-based</td>
<td>↑↑</td>
<td>↓↓</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>– (RCTs)</td>
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<tr>
<td>Non-Ca-based</td>
<td>–</td>
<td>↓↓</td>
<td>↓</td>
<td>–</td>
<td>↑</td>
<td>– (RCT)</td>
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<tr>
<td>Anti-parathyroid drugs</td>
<td></td>
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<tr>
<td>Calcitriol (CTR), alfalcacidol, doxercalciferol</td>
<td>↑↑</td>
<td>↑</td>
<td>↑↑↑</td>
<td>↓↑↑</td>
<td>↓↑↑↑</td>
<td>(Exp)</td>
</tr>
<tr>
<td>Paricalcitol</td>
<td>–</td>
<td>↑</td>
<td>↑</td>
<td>↓↑↑</td>
<td>↓↓</td>
<td>– (no RCT)</td>
</tr>
<tr>
<td>Calcimimetics</td>
<td>↓↓</td>
<td>–</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>– (RCT)</td>
</tr>
</tbody>
</table>

Ca, calcium; P, phosphate; PTH, parathyroid hormone; NA, not available; RCT, randomized clinical trial; Exp, only experimental studies.
effect of vitamin K supplementation on the progression of VC (ClinicalTrials.gov identifier NCT01742273, NCT01528800, NCT00785109, NCT01002157 and NCT01922804).

Bisphosphonates have also been used off label in the treatment of calciphylaxis. In addition to experimental data showing that pamidronate or etidronate prevented VC [37], oral and parenteral etidronate but not all newer generation bisphosphonates have been shown to delay progression of CAC and aortic VC. Since the vascular effects of bisphosphonates cannot be separated from an adequate bone formation, giving these drugs to patients with CKD stage 4/5 may be unsafe.

Sodium thiosulphate has been recently introduced in the armamentarium against calciphylaxis. It may also attenuate the rate of progression of CAC, however at the expense of bone mineral density at the hip site [38].

IS VC SCREENING CURRENTLY JUSTIFIABLE?

Any form of CV calcification is undoubtedly associated with, and predictive of, adverse hard clinical outcomes; nevertheless, for many years, there have been many dilemmas with regard to imaging techniques or quantification scores, radiation hazards, and to whether altering the progression of CV calcification is plausible. For this reason, indiscriminate screening was not recommended (split decision) when the KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention and Treatment of CKD-MBD was published in 2009 [1]. A similar position was later recommended by the American National Kidney Foundation. It should be of note that, in patients with CKD stages 3–5D, plain lateral abdominal RX and echocardiography were considered valid and less expensive alternatives to computed tomography-based imaging techniques to detect and quantify vascular and valvular calcifications [1, 4, 5].

On the other hand, the European Renal Best Practice (ERBP) work group considered a different strategy and concluded that it was justified to screen incident dialysis patients [39], whereas some national guidelines considered it was justifiable to screen any patient with CKD [40]. Furthermore, in the 2009 KDIGO guidelines, it was also suggested that patients with CKD stages 3–5D and with known VC be considered at highest vascular risk (guideline 3.3.2; grade for strength of recommendation 2A), and that ‘it is reasonable to use this information to guide the management of CKD-MBD’ [1]. Even in this prudent guideline it is stated that an assessment for VC is warranted at least in some patients, including ‘any patient in whom the caring physician decides that knowledge of the presence of VC may impact therapeutic decision making’ [1]. Actually, there is a general agreement that VC is an important component of CKD-MBD since animal, epidemiological and observational studies strongly support that VC is not only a mere marker but also a likely cause of increased CV morbidity and mortality in CKD patients. Furthermore, some observational and RCTs have recently corroborated the prognostic relevance of VC and shed some light on several areas of uncertainty highlighted in the 2009 KDIGO guidelines [5].

Finally, it is important to consider that whereas serum biomarkers reflect the risk to which an individual is exposed at the time of measurement, CV imaging represents the cumulative result of prolonged exposure to one or multiple risk factors [5]. As such, different imaging and scores have often been demonstrated to be better outcome predictors than U- or J-shaped risks depicted from serological markers; therefore, imaging allows better CV risk stratification and treatment individualization as VC becomes a new desirable target of therapy [5, 11]. It is not surprising to see as stated above that inclusion of the CAC score significantly improved CV risk prediction beyond traditional CV risk factors in subjects with CKD [12]. All in all, one can conclude that there is a lack of definitive proof that early detection and subsequent tailored treatment based on the presence of CV calcifications leads to improved clinical outcomes. However, based on the Hippocratic principle ‘primum-non-nocere’ and that ample evidence shows that some components of current treatment armamentarium may propagate VC, knowledge of the presence of CV calcification should lead to proper estimation of individual risk assessment and treatment strategy.

CONCLUSION

In summary, CV calcification is a prominent feature of CKD-MBD and is directly linked to dismal clinical outcomes. Consequently, the presence of CV calcification is clinically relevant since there is plenty of new information, confirming that CV calcification is modifiable and that its progression can be attenuated. Moreover, CV calcification evaluation improves risk prediction. We acknowledge that the existing information coming from the CKD and ESRD population does not fulfill WHO requirements for general CV calcification screening recommendation, and that the link between intervention and patient-level outcomes when progression of VC is attenuated has not been conclusively shown. On the other hand, an important independent graded relation between severity of CKD and VC has been clearly demonstrated, and it cannot be denied that VC plays a role in the significant CV morbidity and mortality of CKD patients. Whereas the feasibility of a multi-interventional independent RCTs seems distant, it may be prudent in CKD patients to attempt to lower VC burden, or at least not to increase it, because of health risks and related costs.

Similar to diabetic patients, CKD patients are at high risk of premature CV disease and death, and should be offered the best prevention and treatment. However, as pressure on health resources increases, choices have to be made. Evaluation of CV calcification identifies patients at highest risk. These high-risk patients may benefit most from (i) a lower threshold for performing preventive CV screening procedures; (ii) more intense CV monitoring during episodes of CV stress; (iii) additional initiatives to control traditional and non-traditional CV risk factors and (iv) last but not least less calcifying mineral metabolism treatment regimens. Screening for CV calcification in CKD patients may thus help to offer the best value for the money. Depending on the available resources, screening for CV calcification should be performed in all CKD patients at first presentation and at regular intervals thereafter or only in...
selected cases (e.g. from incident dialysis patients considered for renal transplantation to any patient in whom the caring physician decides that knowledge of the presence of VC may impact a therapeutic decision). Screening for VC fits in the paradigm of personalized medicine; at present not ready for prime time but eager to jump in.

CONFLICT OF INTEREST STATEMENT

J.B. has received speaking honoraria from Abbvie, Amgen, Genzyme and Shire; as a consultant for Abbvie, Amgen, Vifor and Genzyme/Sanoﬁ, and a research grant from Abbvie. P.U.-T. reports personal fees and grants from Amgen, Abbvie, Genzyme–Sanoﬁ, Hemotech and Fresenius. M.V. reports research grants from the Dutch Kidney Foundation, Shire, Abbvie and Sanoﬁ; speaking fees from Amgen and Fresenius and as a consultant from Astellas and Amgen. V.B. reports research grants from Amgen, Bayer and Sanoﬁ, and speaking honoraria from Bayer, Sanoﬁ, Fresenius and Synlap. S.M. has received lecture honoraria from Shire and Amgen. A.C. reports speaking fees from Amgen, Fresenius and Vifor, and as a consultant for FMC. D.G. reports honoraria from Abbvie, Amgen, Fresenius, Keryx and Sandoz. Z.M. has received speaking honoraria from Genzyme/Sanoﬁ, Amgen, FMC, Vifor, Abbvie and Chugai, and research grants from FMC, Baxter, Amgen and Genzyme/Sanoﬁ. M.C. reports lecture honoraria from Abbvie, Shire, Amgen Genzyme and Roche, and research grants from Abbvie and Shire.


REFERENCES

After reading the nicely crafted PRO manuscript of Jordi Bover and colleagues by the CKD-MBD working group of the ERA EDTA, we respectfully maintain our dissent on several major issues of the question at issue. CKD-MBD investigators start by mentioning the CKD-mineral and bone disorder (CKD-MBD) syndrome, a syndrome which the same working group recognized to be of very weak methodological texture in a very recent paper by the same working group [1]. There is no question that ‘intense cross talk exists between the bone and the vasculature’. However, cross talks of similar or greater intensity exist between the heart and the kidney, the kidney and the brain and the liver not to mention the cross talk between the adipose tissue with other organs, from the brain to the bone. CKD is a systemic disease [2] and inappropriately qualifying (i.e. without sound methodology) some of these cross talks as syndromes may hinder scientific research, an issue we discussed elsewhere [3]. Jordy Bover and colleagues review studies showing that cardiovascular calcification is an alteration that can be modified. In our CON manuscript, we summarized the pathobiology of calcium accumulation in the arterial system and showed that inflammation, an early event in human atherosclerosis [4] and a systemic disorder in CKD, has a key role in vascular calcification, which is instead a late event in this process. Vascular calcification is the smog not the fire, thus the problem at issue is not whether vascular calcification is reversible but whether arterial disease leading to vascular calcification is reversible. In the context of today’s knowledge, we (the CON side) believe that hyperparathyroidism and low 1,25 vitamin D are implicated in arterial disease in CKD mainly via mechanisms mediated by inflammation and alterations in the nitric oxide system. We recently showed that osteoblast resistance to PTH in stage 5D CKD patients with peripheral artery disease is a phenomenon strongly associated with inflammation [5], and that vitamin D receptor activation improves nitric oxide-dependent vasodilation in CKD patients [6]. Recent evidence points to high phosphate load per se as a strong pro-inflammatory stimulus in rats with experimental renal failure [7]. Of note, alterations in bone mineral disorders are implicated in atherosclerotic events well beyond CKD. Indeed, in patients with coronary heart disease and in individuals in the general population [8], high serum phosphate and high serum alkaline phosphatase within the normal range of these biomarkers predict a high risk of mortalit...