Myocardial calcification, finally, may foster cardiac electric instability and as such contribute to the disproportionally high incidence of sudden death in CKD. As in burn victims, where initial morbidity is driven by acute skin injury and infection but late long-lasting invalidating complications arise from rigid scar tissue, arterial calcification, initially ignited by disturbed mineral metabolism and inflammation, has severe cardiovascular consequences on its own.

Zoccali and co-workers argue that cardiovascular calcification is not an appropriate target of therapy based on the discrepant findings of intervention studies, since clinical studies did demonstrate attenuated progression of vascular calcification but not improved survival. However, methodological limitations and flaws should be considered a more plausible explanation for this discrepancy.

The interplay between genetic and environmental factors dictates whether cardiovascular calcification will occur or not. Despite its limitations (costs, radiation exposure and low sensitivity), screening for vascular and cardiac valve calcification may allow to identify individuals at risk for premature cardiovascular complications. Since progression of cardiovascular calcification may worsen with inappropriate treatments and it has been shown to be manageable with current tailored therapeutic options, nihilism is not an option. This will require a multifaceted approach in which the control of both mineral metabolism and inflammation are prominent targets. Despite the current lack of hard end point studies supporting this thesis, it should keep in mind that the absence of evidence is not evidence of absence.

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Moderator’s view: Treatment of vascular calcification is a physical impossibility, so far

Christoph Wanner
Division of Nephrology, Department of Medicine, University Hospital of Würzburg, Würzburg, Germany
Correspondence and offprint requests to: Christoph Wanner; E-mail: Wanner_C@ukw.de

In this Polar View, Bover and colleagues [1] review the clinical scenario of vascular calcification including the armamentarium of pharmacological interventions, whereas Zoccali and London [2] more mechanistically describe the complex interplay of the many underlying factors leading to vascular calcification.

At a first glance one may see agreement within the PRO and the CON debate with respect to the widespread interest in the topic, the clinical importance, the many risk factors of vascular calcification and the underlying pathogenesis. There is even consensus about an attractive hypothesis of vascular calcification being a late healing process following inflammation and vascular injury. However, the 360 degree dissent refers to the modifiability and reversibility of the calcified road we travel every day, in every dialysis unit, dazzled by smog after the fire. The dissent extends on the systematic screening for vascular calcification in CKD patients without any consequence and in the absence of an effective intervention improving outcome.

One may argue that the knowledge about distinct vascular and valvular calcifications can be used for stratifying cardiovascular risk and predicting prognosis, at least in selected individuals.

But why screening at all, if we have no pharmacological treatments available that may reverse the process and improve clinical outcomes? The key question raised in the PRO debate, whether screening of vascular calcification will ultimately translate into better outcomes, remained unanswered. Observational studies raise speculations but are unable to answer this question. Prospective randomized controlled trials are scarce.

Targeting phosphate and PTH with the use of phosphate binders or a calcimimetic has not produced positive outcome results into randomized clinical trials but data from large scale studies with calcidiol or vitamin D receptor activators are completely lacking. By consensus, many nephrologists today prescribe moderate intensity drug treatment and patients follow the recommendations with moderate compliance. We
intend to correct laboratory values and aim to avoid surgery or extreme pathologies using drug treatment. No case can be made on the basis of the current data for routine use or high intensity treatment of selected interventions.

For example, KDIGO has recently selectively updated the 2009 CKD MBD guidelines (available January 2015 for public review). Based on the available evidence, the updated 12 and most of the 27 old guidelines resulted in a level 2 strength of recommendation and grade C or D for the quality of supporting evidence. KDIGO reminds that the true effect of all suggestions may be substantially different from the estimate of the effect (grade C) or that the estimate of effect is very uncertain, and often will be far from the truth (grade D). Different choices will be appropriate for different patients, and each patient needs help to arrive at a management decision consistent with her or his values and preferences (level 2). Clearly, the goal of grades C and D is guidance and there is no room for overinterpretation through industrial channels [3].

Despite enthusiasm for vascular calcification screening and personalized medicine by Bover et al., there is also a word of regret that we are distant from further multi-interventional independent randomized controlled trials. One may also argue that previous trials could not, or were not, adequately designed with sufficient sample size and statistical power to detect a positive signal. Many risk factors are present and many pathways are activated producing different outcomes. Multiple interventions may be necessary to target the appropriate underlying factor responsible for the respective outcome. Zoccali and London reject the view that a calcified vessel is an appropriate target for current interventions. Oxidative stress and inflammation, detectable by many activated acute-phase proteins, have injured the vessel wall and calcifying healing processes are underway. Uncertainty exists further, as to whether we are at present able to control the processes leading to telomere shortening, cellular senescence and accelerated ageing?

Currently, there is no way out of this dispute without further testing, prospectively in controlled studies and including a randomized intervention and targeting the appropriate outcome parameter.

Thus, at the end of reading the PRO debate one may realize that we have added another enthusiastic review to the 1296 hits obtained by literature search [1]. Equally, or more importantly, we also hear a critical voice [con debate, 2] which recommends abandoning a territory where scientific research deviates towards groundless pathways.

CONFLICT OF INTEREST STATEMENT

The author declares having received consultancy honoraria from Amgen.

(See related article by Zoccali and London. Con: Vascular calcification is a surrogate marker, but not the cause of ongoing vascular disease, and it is not a treatment target in chronic kidney disease. Nephrol Dial Transplant 2015; 30: 352–357; See related article by Bover et al. Pro: Cardiovascular calcifications are clinically relevant. Nephrol Dial Transplant 2015; 30: 345–351.)

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