

these unexpected results. We are also questioning about differences in the PB medication among the 11 participating countries.

After investigating the reasons for the very low numbers of PB prescription, we strongly suggest a separate analysis of the patients on the basis of the PB medications and the serum phosphate level to understand the association of these parameters with the outcomes. Apart from some particular dialysis schedule including long and/or daily strategies, phosphataemia remains an important marker of nutrition in cases of conventional HD. The use of PBs could be associated with a better outcome when associated with a higher protein intake, but this remains a speculation.

We encourage the ARO investigators to provide more observational data from European countries to improve our understanding of the association between mineral metabolism disorders, their treatments and outcomes.

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1. Floege J, Kim J, Ireland E *et al.* Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population. *Nephrol Dial Transplant* 2010; doi:10.1093.ndt/gfq1219
2. Tentori F, Blayney MJ, Albert JM *et al.* Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the dialysis outcomes and practice patterns study (DOPPS). *Am J Kidney Dis* 2008; 52: 519–530
3. Kalantar-Zadeh K, Kuwae N, Regidor DL *et al.* Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int* 2006; 70: 771–780
4. Jean G, Vanel T, Terrat JC *et al.* Treating mineral metabolism disorders in patients undergoing long hemodialysis: a search for an optimal strategy. *Hemodial Int* 2009; 13: 526–532

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Reply

Jean and Vanel raise some interesting questions about the management of dialysis patients in Europe and the association between phosphorous and mortality, especially when considering the use of phosphate binders. In the ARO population, the majority of patients (>80% in all countries) have three dialysis sessions per week, with the median duration of each session being 4 h. Unfortunately, ARO does not contain data allowing us to estimate dietary phosphate intake. We cannot fully exclude underreporting of phosphate binder use in some countries. Moreover, dosing equivalence between different phosphate binders used in this cohort, which is really difficult to establish, prevented us from looking at a dose-dependent effect. However, we found no relationship between the prevalence of phosphate binder use and phosphate levels at baseline.

Table 1. Association between phosphate levels and mortality in the ARO population according to whether or not a participant is taking a phosphate binder at baseline

Phosphate (mmol/L)	Adjusted HR (95% CI) ^a	
	Not taking phosphate binders	Taking phosphate binders
<1.13	1.29 (1.08–1.55)	1.00 (0.75–1.34)
1.13–1.78	1	1
>1.78	1.32 (1.07–1.64)	1.33 (1.04–1.71)

^aAdjusted for demographics (age, gender, country, body mass index/BMI, smoking status), medical history (chronic kidney disease aetiology, history of diabetes, history of cardiovascular disease (CVD), history of Cancer), dialysis parameters (vintage, vascular access type, Kt/V, blood flow), markers of inflammation (serum albumin, C-reactive protein), CVD medications (antihypertensive drugs, ACE inhibitors, oral anticoagulants, anti-aggregants), vitamin D use and other lab parameters (PTH, calcium, haemoglobin/Hb, ferritin, cholesterol, blood leucocytes) and miscellaneous (hospitalization, change in vascular access type).

In our population, we observed a significant interaction between phosphate level, phosphate binder use and mortality ($P = 0.02$). As can be seen in Table 1, this interaction is being driven by the lack of an association between low phosphate levels and mortality in those treated with a phosphate binder compared to those untreated.

In principle, this observation is consistent with the data of Isakova *et al.* [1], who noted a reduced mortality in haemodialysis patients treated with a phosphate binder. However, in that study, most of the benefit was observed in patients with high phosphate levels, whereas in our study patients treated to low phosphate levels appeared to benefit most from a phosphate binder.

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1. Isakova T, Gutiérrez OM, Chang Y *et al.* Phosphorus binders and survival on hemodialysis. *J Am Soc Nephrol* 2009; 20: 388–396

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Is there a link between thrombotic thrombocytopenic purpura and anti-glomerular basement membrane disease?

Sir,

We read with interest the article by Torok *et al.* [1]. They reported a 43-year-old Caucasian male who had developed thrombotic thrombocytopenic purpura (TTP) followed by anti-glomerular basement membrane (anti-GBM) disease

[1]. They described that multiple autoimmune diseases could occur in the same patient as the theory of a 'mosaic of autoimmunity' but did not suggest the possible mechanisms [1].

Although not extensively studied yet, we speculate that the helper T (Th) cell-associated cytokine, interleukin (IL)-12, might be involved in the common pathogenesis between the two diseases [2,3]. Takatsuka *et al.* [2] showed that the patients with thrombotic microangiopathy had a significant increase of IL-12 at the time of leukocyte recovery after bone marrow transplantation (BMT) ($P < 0.05$), while none of the patients without microangiopathy showed an increase of IL-12. Kakishita also reported that TTP and haemolytic uraemic syndrome (HUS) after BMT might be predicted at an early stage by determining any increase in plasma IL-12 at the time of leukocyte recovery [3], suggesting the possibility that TTP might be related to inflammation or autoimmunity.

In addition, Kalluri *et al.* [4] developed a new mouse model of human anti-GBM disease, in which crescentic glomerulonephritis and lung haemorrhage were associated with the emergence of an IL-12/Th1-like T-cell phenotype. Conversely, Kitching *et al.* [5] demonstrated that IL-12p40^{-/-} knockout mice were protected from renal injury in an experimental model of autoimmune anti-GBM glomerulonephritis.

Therefore, there is a possibility that IL-12 might play an important role in the development of both TTP and anti-GBM disease and it would be interesting to measure IL-12 during the course of the disease in the patient of Torok *et al.* [1].

However, further studies are necessary to elucidate whether IL-12 is elevated in all kinds of TTP or HUS and whether it might also play an important role in the development of human anti-GBM disease. The relationship between IL-12 levels and the degree of ADAMTS13 deficiency or the titres of anti-GBM antibody should be further evaluated in the future.

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1. Torok N, Niazi M, Al Ahwel Y *et al.* Thrombotic thrombocytopenic purpura associated with anti-glomerular basement membrane disease. *Nephrol Dial Transplant* 2010; 25: 3446–3449
2. Takatsuka H, Takemoto Y, Okamoto T *et al.* Thrombotic microangiopathy following allogeneic bone marrow transplantation. *Bone Marrow Transplant* 1999; 24: 303–306
3. Kakishita E. Pathophysiology and treatment of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS). *Int J Hematol* 2000; 71: 320–327
4. Kalluri R, Danoff TM, Okada H *et al.* Susceptibility to anti-glomerular basement membrane disease and Goodpasture syndrome is linked to MHC class II genes and the emergence of T cell-mediated immunity in mice. *J Clin Invest* 1997; 100: 2263–2275

5. Kitching AR, Turner AL, Semple T *et al.* Experimental autoimmune anti-glomerular basement membrane glomerulonephritis: a protective role for IFN-gamma. *J Am Soc Nephrol* 2004; 15: 1764–1774

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Reply

Sir,
Shin *et al.* letter lends an important perspective on a critical topic. We previously reported the simultaneous presentation of thrombotic thrombocytopenic purpura (TTP) and Goodpasture's disease in the same patient. We agree completely that the pathogenic mechanism of TTP and Goodpasture's disease was not identified in our case. We speculated the 'mosaic of autoimmunity' theory as an explanation of this association based on the accumulating evidence of the autoimmune nature of TTP [1] and Goodpasture's disease.

However, transplant associated thrombotic microangiopathy (TA-TMA) is a different entity from TTP [2]. Pathologically, the thrombi in TA-TMA contain both fibrin and von Willebrand Factor, whereas in TTP, the thrombi consist mainly of platelets [3]. Suggesting that these diseases are different, this makes us believe that the underlying pathologic mechanisms might also be different. Besides, TA-TMA can be related to other causes, like Graft Versus Host Disease, to immunosuppressive medications side-effects and to viral infections which all can mimic TTP [4]. Therefore, high IL-12 levels preceding TA-TMA might not exactly fit TTP. Nevertheless, we still feel that it is interesting to extend this observation to TTP, and further studies are thus needed. Concerning Goodpasture's disease, the interest has been shifted to IL-23 by Kitching *et al.*, the same group who reported the protective role of IL-12 in the experimental knockout mouse model against the development of the disease [5]. In our case report, we did not have baseline IL-12 levels before or during the disease activity, which makes it impossible to confirm or dispute the relation between IL-12 and these entities.

We share the conclusion of Kim *et al.* that further research focusing on the possible autoimmune mechanisms in TTP and anti-GBM disease, specifically the relation with IL-12, is needed. What we know about these intriguing entities is less than what we do not know.

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1. Coppo P, Bengoufa D, Veyradier A *et al.* Microangiopathies Thrombotiques de l'Adulte. Severe ADAMTS13 deficiency in adult idiopathic thrombotic microangiopathies defines a subset of patients characterized by various autoimmune manifestations, lower platelet count, and mild renal involvement. *Medicine (Baltimore)* 2004; 83: 233–244