Editorial Commentary

Does alfacalcidol reduce cardiovascular complications in hemodialysis patients?

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Provenance: This is an invited article commissioned by the Section Editor Wei Liu, MD (Department of Nephrology, The Affiliated Anqing Hospital of Anhui Medical University, Anqing, China).

Comment on: J-DAVID Investigators, Shoji T, Inaba M, *et al.* Effect of Oral Alfacalcidol on Clinical Outcomes in Patients Without Secondary Hyperparathyroidism Receiving Maintenance Hemodialysis: The J-DAVID Randomized Clinical Trial. JAMA 2018;320:2325-34.

Submitted Feb 28, 2019. Accepted for publication Mar 11, 2019.
doi: 10.21037/atm.2019.03.26
View this article at: http://dx.doi.org/10.21037/atm.2019.03.26

Cardiovascular disease is a major health burden in chronic kidney disease (CKD) populations. Indeed, individuals with end-stage renal disease (ESRD) have a 6- to 8-fold increase in mortality compared to the general population, half of which is caused by cardiovascular disease (1). The mineral and bone disorder of CKD (CKD-MBD), which also includes vascular calcification, contributes to these cardiovascular complications (2). It is well recognized that advanced CKD prevents the renal 1alpha-hydroxylation of vitamin D into its active form, 1,25-dihydroxyvitamin D (calcitriol; 1,25-OH-D) leading to low levels of 1,25-OH-D in ESRD patients (3). This deficiency accentuates secondary hyperparathyroidism (SHPT) and has been proposed to contribute to left ventricular hypertrophy, infections, insulin resistance and anemia in CKD populations (4). Supplementation with active vitamin D or vitamin D receptors analogs (VDRAs) has therefore been suggested to partially restore mineral homeostasis and reduce the burden of cardiovascular disease in individuals suffering from advanced CKD.

Over the past decades, multiple studies investigated whether VDRA could benefit individuals with advanced CKD. A meta-analysis including 76 randomized clinical trials reported that VDRA usage decreased parathyroid hormone (PTH) levels compared to placebo (5). As expected, VDRA usage was also associated with increased blood phosphate and calcium levels. In animal models, VDRA administration has been shown to reduce left ventricular hypertrophy and protect against vascular calcification by increasing Klotho expression in the vasculature (6-8). In contrast, high doses of VDRAs promote vascular calcification and induce bone mineralization defects by increasing the expression of Wnt pathway inhibitors (9-11). In clinical trials such as PRIMO and OPERA, VDRA use had no significant effect on left ventricular mass, arterial stiffness or endothelial function but was associated with reduced cardiovascular hospitalizations (12-15). Several observational studies have then investigated the effect of VDRA on cardiovascular endpoints and mortality. In these studies, VDRA usage was associated with increased survival and decreased cardiovascular events in dialysis patients regardless of the PTH level, strengthening the hypothesis that VDRA could improve cardiovascular health independently of its PTH lowering effects (16-18). However, such observational studies are prone to indication bias and these findings have not been replicated in large scale randomized clinical trials. Until now, whether VDRAs are beneficial to dialysis individuals in terms of cardiovascular and all-cause mortality remains uncertain.

To fill this knowledge gap, Shoji and colleagues recently published a randomized clinical trial comparing oral alfacalcidol *vs.* usual care in a dialysis population (19). Between 2008 and 2011, they recruited adult hemodialysis patients from 207 Japanese dialysis centers. Participants had to have stable levels of serum calcium and phosphate, and intact PTH levels under 18.9 pmol/L (180 pg/mL)

without the use of VDRA in the prior four weeks. Individuals were randomized 1:1 to a starting dose of 0.5 μg of oral alfacalcidol daily *vs.* usual care using stratified blocks for age, sex, diabetic nephropathy, cardiovascular disease, and dialysis vintage. The maximal alfacalcidol dose was 7 μg/week to achieve biochemical targets according to the *Japanese Society for Dialysis Therapy guidelines*. The use of phosphate binders, cinacalcet or/and alimentary interventions was allowed as needed and alfacalcidol doses could be reduced or withdrawn if necessary. Uncontrolled SHPT was treated with substitution to another oral or intravenous VDRA in the treatment group or addition of a VDRA in the control group. A VDRA substitution/interruption or addition for 12 or more consecutive weeks was considered as a dropout. Individuals were followed for more than 48 months for primary, secondary, laboratory and safety outcomes. The primary outcome was a composite of fatal or non-fatal cardiovascular events. The secondary outcome was all-cause mortality and pre-specified safety outcomes (cardiovascular events, infections, neoplasia, and falls/fractures). While individuals were not blinded to their treatment assignation, adjudication of outcomes was performed by a blinded committee.

After screening, 495 individuals were assigned to alfacalcidol *vs.* 481 to usual care. Included individuals had a mean age of 65 years, a mean dialysis vintage of 5.5 years, were 60% male and 25% had a history of cardiovascular disease. Mean intact PTH levels at baseline was 9.03 pmol/L (86 pg/mL). There were 32.4% (treatment group) and 35.5% (control group) of the individuals who interrupted the assigned intervention and were considered as dropouts. In the intention to treat analysis, there was no significant difference in the primary outcome of composite cardiovascular events (HR 1.25; 95% CI, 0.94 to 1.67) and all-cause mortality (HR 1.12; 95% CI, 0.83 to 1.52) between groups. While *per-protocol* analyses yielded similar results, the signal toward increased events with alfacalcidol was amplified for cardiovascular events (HR 1.32; 95% CI, 0.96 to 1.81) and attenuated for all-cause mortality (HR 0.98; 95% CI, 0.70 to 1.38). Adjustment for baseline characteristics or geographical origin of patients did not alter these results.

The J-DAVID trial has several strengths. Its authors aimed at evaluating the cardiovascular effects of vitamin D analogs in dialysis patients, for which evidence from randomized clinical trials is lacking. They conducted a randomized trial including a large number of dialysis patients, which is rare in the nephrology field. Another strength of the J-DAVID study comes from its rigorous trial methodology that included a stratified randomization scheme yielding balanced baseline characteristics between groups. Furthermore, while blinding participants to their assignation was not possible for operational and ethical reasons, the adjudication of primary, secondary and safety outcomes was blinded to treatment assignation. Finally, they meticulously explored two per-protocol sets definitions and used adjusted models to test the robustness of their findings to individuals' baseline differences and geographical repartition.

Nevertheless, the major limitation of the J-DAVID study is its generalizability. Indeed, the trial was restricted to individuals with normal PTH levels. Because Japanese and international guidelines recommend the use of VDRA to reduce PTH levels in individuals with SHPT (2,20), the authors restricted their study to a population for which VDRA would have not been routinely used. The trial's investigators relied on the results of a previous observational study that showed similar survival benefits of VDRA at low and high PTH levels to support their decision of excluding individuals with high PTH levels (16). Even if advanced statistical tools such as marginal structural models were used to minimize the risk of confounding, the latter study reported the 2-year survival of incident dialysis patients in the United States. This observational study's population and outcomes were thus radically different from those of J-DAVID. These differences could explain the results discrepancies between previous results and the J-DAVID's findings. Furthermore, individuals included in J-DAVID had a long dialysis vintage (mean 6 years) and a low prevalence of cardiovascular disease (25%). These characteristics are radically different from those of European and American patients who have lower dialysis vintages and a much higher prevalence of cardiovascular disease (21). Therefore, individuals included in J-DAVID were in a much better health condition than most of the occidental dialysis patients, which also limits the generalizability of its results. Further particularities of this study are the target range for PTH levels (between 60 and 240 pg/mL), the highly prevalent use of carbonate calcium (83%) and the high calcium dialysate concentrations (69% with 3.0 mEq/L and 26% with 2.5 mEq/L). These clinical practices differ from occidental ones, where guidelines advise a PTH target between 2 to 9 times upper normal limit, the restriction of carbonate calcium use and use of lower calcium dialysate concentrations (2). This higher calcium load could also partly explain the increased cardiovascular events in the

treatment group. Finally, the J-DAVID trial was conducted in an exclusively Japanese population, in which there are known Vitamin D receptor (VDR) polymorphisms (22). Some of these polymorphisms have been associated with altered Vitamin D response (23) or changes in mineral metabolism in CKD (24,25) that may further limit the applicability of these results to other populations. Taken together, these populational, biochemical and clinical differences between J-DAVID participants and most of the occidental dialysis patients should refrain prompt generalization of these results to other populations.

Another limitation of the J-DAVID trial is the relatively high number of dropouts (32% *vs.* 36%). While a certain number of dropouts was expected considering the trial duration and the clinical need to control biochemical parameters, these high dropout counts contrast with the low prevalence of laboratory abnormalities which could have warranted discontinuation of assigned treatment. Furthermore, reasons for discontinuation were not collected, yielding additional uncertainty about treatment adherence. To address this issue, authors conducted two sets of *per-protocol* analyses that excluded all dropouts, except for individuals that switched from alfacalcidol to another VDRA in the treatment group which were kept in the second analysis. These two analyses resulted in similar non-significant effects of alfacalcidol on the primary and secondary outcomes but amplified the trend toward increased cardiovascular events with alfacalcidol. Whether these results truly represent a harm associated with alfacalcidol or an attrition bias expected with *per-protocol* analyses remains unclear. Advanced statistical models with time-varying exposures, which could have helped to resolve this uncertainty, were not conducted by investigators. In addition to the important dropout rate, the J-DAVID trial was also limited by a relative lack of statistical power. Indeed, as investigators expected a primary outcome cumulative incidence of 28% to 32% over 48 months of follow-up, incidences of only 18% and 21% were obtained. While this lower than expected rate of cardiovascular events reflects a welcomed improvement in outcomes of dialysis patients, it also lowered the trial's statistical power to detect a beneficial or harmful effect of VDRA. Nevertheless, it is possible that the non-significant signal toward increased cardiovascular events in the treatment group could have become significant if a higher number of individuals had been recruited or if a higher global rate of cardiovascular events had been observed. Clearly, caution should be taken when interpreting the non-conclusive results of this trial.

In conclusion, the J-DAVID trial has the merit to be one of the rare RCTs conducted in the dialysis population. It showed that alfacalcidol use, when compared to usual care, is not associated with decreased cardiovascular events. Its restriction to Japanese individuals with normal PTH levels, low cardiovascular disease prevalence, long dialysis vintage and high calcium load limits its generalizability to other populations and may explain the results' discrepancies from previous observational studies. Because VDRAs are not routinely used in individuals without SHPT, the J-DAVID trial is unlikely to change clinical practice. Still, the observed signal towards increased cardiovascular events in J-DAVID is concerning. Whether such a trend would be observed in populations with a higher prevalence of cardiovascular disease is unknown. J-DAVID's results mandate additional clinical trials to identify the populations in which the PTH-lowering benefit of VDRAs may be overcome by their potential harmful cardiovascular effects. While J-DAVID results are clearly not definitive, they must increase clinicians' awareness of the potential benefits and harms of VDRAs in dialysis patients.

Acknowledgements

Funding: This work was supported by the Canadian Institutes of Health Research (CIHR); the *Fonds de Recherche du Québec-Santé* (grant number 32661); the KRESCENT program from the CIHR, Canadian Society of Nephrology and Kidney Foundation of Canada (grant number 150006); the Laval University Faculty of Medicine and the *Fondation du CHU de Québec – Université Laval*.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Desbiens LC, Mac-Way F. Does alfacalcidol reduce cardiovascular complications in hemodialysis patients? Ann Transl Med 2019;7(8):167. doi: 10.21037/atm.2019.03.26

