Mortality reduction by vitamin D receptor activation in end-stage renal disease: a commentary on the robustness of current data

Marc G. Vervloet¹ and Jos W. R. Twisk²

¹Department of Nephrology and ²Department of Epidemiology and Biostatistics, VU University Medical Center, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

Abstract

Background. Debate exists about assumed mortality effects of the use of vitamin D receptor activators (VDRA) in haemodialysis patients.

Methods. In the absence of randomized controlled trials (RCTs), current knowledge comes from several large observational studies that examined the association between the use of VDRA and mortality. In these trials, modern but complicated statistical analysis has been performed, attempting to minimize potential bias of suboptimal study design. This complexity may lead to suspicion about study results, and for this reason these results may be discarded for everyday clinical practice.

Results. In the current commentary, several crucial aspects of applied statistics are highlighted, attempting to aid practicing clinicians to properly weigh these study results in a balanced way. The difference between historical and retrospective cohort analysis is addressed, as well as the use of sensitivity analysis and propensity scores. The impact of confounding, mediation and effect modification for these studies on VDRA use is discussed.

Conclusions. It is concluded that the results from these studies appear quite robust and consistent. Furthermore, there is an increasing amount of data from experimental data suggesting mechanisms for observed beneficial effects. However, it must be kept in mind that VDRA can have adverse effects and that observational data can never replace RCTs.

Keywords: clinical trials; methodology; mortality; vitamin D receptor activation

Introduction

For decades, the role of vitamin D receptor activator (VDRA) in ameliorating hyperparathyroidism and hypocalcaemia in severe kidney failure and end-stage renal disease (ESRD) has been acknowledged. Because of reduced renal 1α-hydroxylase activity, an activated vitamin D analog is prescribed (calcitriol, doxercalciferol, paricalcitol or alfacalcidol). Recently, an analysis of a large cohort of haemodialysis patients from the USA demonstrated that the use of a VDRA was associated with a reduced mortality when compared with non-users of any VDRA [1]. Most intriguing was the fact that, using complex statistical methodology in an attempt to dissect the causes of this improved mortality, the favourable outcome of patients on VDRA could only partly be attributed to improvements in biochemical markers of mineral and bone disease. This has set the field on fire and has led to an increased scientific interest in assumed biological and physiological mechanisms of VDRA, beyond its well-defined effects on bone and mineral metabolism. On top of that, in several other cohorts, comparable results were achieved, using comparable methods [2–5]. Very recent meta-analyses on the question of mortality effects of VDRA either questioned [6] or confirmed [7] its favourable effects. This leaves the practicing nephrologist with the question: Is the currently available level of evidence enough to change clinical practice, i.e. should a VDRA be prescribed to ESRD patients, regardless of their level of PTH, calcium, or phosphate? Doubt arises from the well-recognized limitation of these studies: they compared groups that were not randomized, and therefore leave the potential for unrecognized differences between groups that accounted for observed differences in the outcome.

A definite answer to this question should ideally come from prospective randomized controlled trials (RCT). These trials with regard to mortality effects of VDRA in ESRD patients are lacking, and therefore current knowledge and opinion are based on observational data. Although there are an ever-increasing amount of data demonstrating potential mechanisms that might contribute to the observed improved patient outcome [8], the vast majority of these data come from animal studies or in vitro experiments. For these reasons, the potential benefit of VDRA is debated, the indications for its use have become more vague and the probability of VDRA use in the presence of a relative contra-indication like hypercalcaemia has increased. However, a meticulous appreciation of available data from observational studies, instead of a complete dismissal of it, might prevent the loss of important clues to clinical nephrology or delay its application for years. Therefore, in the current commentary, we attempt to critically consider the large observational studies that examined the role...
of VDRA on mortality in patients with ESRD on dialysis from an epidemiological view.

Patients and methods

Historical cohort study versus retrospective cohort study
One of the major points in the discussion regarding the possible positive effects of VDRA is the fact that the most important data come from a historical cohort study [1,9]. The problem is that a historical cohort study is often confused with a retrospective cohort study. In a retrospective cohort study, the information is gathered retrospectively, which means that the obtained information is fairly unreliable. In a historical cohort on the other hand, the information is not gathered retrospectively, but prospectively. In other words, in a historical cohort study information is used that is gathered some time ago. Because of this, the information used in a historical cohort study is much more reliable than the information of a retrospective cohort study. One of the problems of a historical cohort study on the other hand is that the information to be used is that which is available at the time of measurement and sometimes that information is not complete. Therefore, it is possible that there are unknown differences between groups that are responsible for the observed effects. With a retrospective cohort study, the problem of non-complete information is less prominent, because the researchers are able to get all the relevant information, however, as mentioned before, in a fairly unreliable way. All the current large observational studies on VDRA in ESRD [1–5], which are the focus of this commentary, are historical cohort analyses. So the positive effects of VDRA use on both cardiovascular and all-cause mortality reported in the historical cohort study by any of these can be partly caused by the unobserved difference between groups. One of the possibilities of dealing with the potential problem is the use of sensitivity analyses.

Sensitivity analyses
With sensitivity analyses, the data are reanalysed to explore the robustness of the results. This can be done by changing data, relaxing assumptions or by analysis of subgroups. When all analyses lead to more or less the same result, the results of the primary analysis are robust and therefore reliable. In the study by Teng et al. [1] for instance, sensitivity analyses were performed on subgroups with a different initial survival time. Because all results were more or less comparable, the positive effects of VDRA that have been found in this particular study seem to be quite robust.

The use of complicated statistical analyses
One of the problems that arise when many sensitivity analyses are done is that the majority of researchers or clinicians do not understand it anymore. When the statistics become complicated and difficult to understand, the results of the particular study are not trusted anymore, especially when the results of the study are somewhat controversial. This is one of the main methodological issues in the VDRA discussion; the statistics used in the studies that show a positive effect of VDRA are complicated. In most observational studies, due to the longitudinal nature of the studies, the effect of time-varying covariates is investigated [1–5,9] and different weights in marginal structural models [1] and generalized estimating equations [2] are used. All these techniques are quite relevant, but because they are complicated and sometimes not interpreted in the proper way [2], they seem suspicious.

The use of propensity scores
One of these complicated issues is for instance the use of propensity scores. In a propensity score, the information of several potential confounders is combined into one score. Propensity scores are therefore mostly used in small observational studies (or in large studies with not many events) to decrease the number of potential confounders. In the study of Teng et al. [1], propensity scores were used, even though the study population was huge and the number of events was rather high. In other words, although it was not wrong, it was not necessary to use propensity scores in this study. Again, because many researchers and clinicians do not really understand what a propensity score is, its use leads to suspicion regarding the results of the study.

Confounding and mediation
In many of the observational studies that show a positive effect of VDRA use, time-varying covariates are used [1,2,4,5]. The use of time-varying covariates is important to investigate possible mediating effects of these covariates. In light of this, a strong distinction must be made between confounding and mediation. Both a confounder and a mediator are related to the central determinant (i.e. VDRA use), and they are also related to the outcome of the study (in this respect mostly death). The difference between the two depends on whether or not the particular variable is in the causal pathway. Age, for instance, is a typical confounder because it is mostly related to VDRA use, it is certainly related to mortality and it is not in the causal pathway. A way to deal with confounders is to adjust for them, and in none of the large observed cohorts [1–5], did this change the conclusions from the unadjusted results.

PTH on the other hand is a typical mediator; PTH is related to VDRA use, it is related to mortality and it is probably in the causal pathway [10,11]. Also calcium and phosphate might be in the causal pathway and might themselves influence mortality [5,12]. It is possible that due to VDRA use, PTH levels decrease and therefore the probability of dying is lower. The problem with confounding and mediation is that within regression analysis they are investigated in exactly the same way. First a ‘crude’ effect is estimated (an analysis with only the use of VDRA as determinant), and secondly an ‘adjusted’ effect is estimated (an analysis where the potential confounder or mediator is added to the regression model). In both adjusted analysis, the effect of VDRA (for instance the HR when Cox regression analysis is performed) has to be compared with the effect of VDRA from the ‘crude’ analysis. It is crucial that both differences in effect between the ‘crude’ and
‘adjusted’ analysis have to be interpreted differently. When the age-adjusted effect of VDRA is much lower than the ‘crude’ effect of VDRA, it means that part of the effect of VDRA is caused by age (VDRA being more prescribed to younger patients). The ‘real’ effect of VDRA is therefore the age-adjusted effect. When the PTH-adjusted effect of VDRA is (much) lower than the ‘crude’ effect of VDRA, it means that part of the effect of VDRA goes through PTH. In this situation, the ‘real’ effect of VDRA is the ‘crude’ effect and there is some additional information about the part of the effect that goes through the mediator. The difference between confounding and mediation is often difficult, which complicates the interpretation of adjusted/multiple regression analysis. To investigate possible mediation, time-varying covariates are very useful, because when a variable is in the causal pathway, there has to be some time lag between the determinant and the mediator. Surprisingly, however, in the study of Teng et al. [1], there was no mediating effect of either PTH, phosphorus or calcium. So there must be another mechanism that is responsible for the positive effects of VDRA use. In many studies [2,4,5], possible confounding variables and mediation variables are analysed together, which makes it even more difficult to obtain the ‘real’ effect of VDRA use.

Effect modification

Both mediation and confounding should be further distinguished from effect modification. Effect modification means that the effect of VDRA is different, for instance for males versus females, older versus younger patients, etc. Effect modification can be investigated by adding interaction terms (i.e. multiplication between the central determinant and the potential effect modifier) to the multiple regression models. When there is significant effect modification, the results should be presented as subgroup specific. Another way to examine possible effect modification is to perform stratified analysis. This was performed by Teng et al. [1], but again, when comparing only 

Association versus prediction models

Another issue in multiple regression analysis is the difference between association models and prediction models. With an association model, the researcher is interested in the effect of one central determinant (such as VDRA use) and the effect of the central determinant is estimated in the best possible way (i.e., by investigating confounding, effect modification and mediation). With a prediction model, however, the researcher is interested in the best (and most simple) combination of variables that can predict the outcome. In that situation, the researcher is not specifically interested in one central determinant, such as VDRA, but in all possible predictor variables. The problem is that the statistical modelling process is totally different for building an association model than for building a prediction model.

In the latter, for instance, backward and/or forward selection procedures can play a role. It should be obvious that in studies where the effect of VDRA is investigated, an association modelling procedure should be used. Unfortunately, this is not always the case. For instance, in the study of Shoji et al. [3], a prediction modelling procedure is used in a situation where the authors should have used an association modelling procedure, and although VDRA use was still present in the final prediction model, that results should be interpreted with caution.

Conclusion

In conclusion, the results of the observational studies that show a positive effect of VDRA in dialysis patients seem to be quite robust and therefore reliable. The biggest problem is the possibility of unknown differences between compared groups, which is due to the historical cohort design used. In the absence of prospective randomized trials, two other pieces of information are important for the clinician to decide whether or not to change every day practice. The first is the presence of a plausible mechanism that might explain the observed benefit of VDRA use in patients on dialysis and the second is to address the potential of doing harm by VDRA.

Several studies found effects of VDRA beyond its ‘traditional’ role in bone and mineral metabolism. The renin biosynthesis can be inhibited [13,14], possibly explaining part of observed effects of vitamin D metabolites on arterial function [15]. VDRA has a positive impact on left ventricular abnormalities in rats [16] and myocardial hypertrophy in haemodialysis patients [17]. In young haemodialysis patients, it was shown that calcitriol attenuates insulin resistance, improved insulin secretion on an oral glucose load and improved hypertriglyceridaemia [18]. These and other potential mechanisms, as recently reviewed [19], all suggest mechanisms for an improved cardiovascular outcome in patients on dialysis. Besides its potential beneficial effects on cardiovascular events, VDRA has a potential positive impact on immune function [20,21], and it is suggested that supplementation of vitamin D is associated with reduced incidence of colorectal cancer [22]. These and even several other mechanisms [8] all could explain part of the beneficial effects of VDRA, beyond its traditional effects on bone and mineral metabolism.

When considering potential toxicity while prescribing VDRA, it is important to realize that the safe upper dose level of calcidiol has not been established [23]. In renal failure, usually active vitamin D is used, instead of calcidiol, so one must be cautious while interpreting data about safe doses. However, for any metabolite or analogue of vitamin D, hypercalcaemia is the hallmark of toxicity. There is some concern that calcitriol, via induction of hypercalcaemia, might contribute to vascular or cardiac calcifications [24]. There are no data that currently used doses of VDRA themselves contribute to the process of vascular calcification, but the hypercalcaemia or positive calcium balance induced by vitamin D supplementation probably does [25].

Although all data considering mortality effects of VDRA in haemodialysis patients come from historical cohort
analyses, it is inconsiderate to dismiss these results entirely. As discussed, within each of these observational studies [1–5], methods used are robust; sensitivity analyses, including subgroup analysis, all point to the same conclusion. The results between studies, in different populations, are consistent. There are numerous studies that provide rational explanations for the observed improved outcome for dialysis patients treated with VDRA. It is prudent to prevent hypercalcaemia, but there are no known levels above which VDRA has to be interrupted. It is probably also prudent to avoid excessive intake of calcium, because the serum calcium concentration does not necessarily reflect the calcium balance. For these reasons, one might argue that it is reasonable to prescribe a VDR activator to all dialysis patients, while restricting calcium intake, unless hypercalcaemia develops. However, the ultimate answer to the discussion of whether or not VDRA has beneficial effects in haemodialysis patients treated with VDRA analogs. It is prudent to prevent excessive intake of calcium, because the serum calcium concentration does not necessarily reflect the calcium balance. For these reasons, one might argue that it is reasonable to prescribe a VDR activator to all dialysis patients, while restricting calcium intake, unless hypercalcaemia develops. However, the ultimate answer to the discussion of whether or not VDRA has beneficial effects in haemodialysis patients has to be obtained from a randomized controlled trial.

Conflict of interest statement. M.V. has participated in advisory boards and received research funding from Abbott. JT reports no conflicts of interest. (See related article by F. Tentori et al. The survival advantage for haemodialysis patients taking vitamin D is questioned: findings from the Dialysis Outcomes and Practice Patterns Study. Nephrol Dial Transplant 2009; 24: 963–972.)

References