Shoji et al. Renal Replacement Therapy (2016) 2:19
DOI 10.1186/s41100-016-0029-z

Renal Replacement Therapy

RESEARCH Open Access

# Vitamin D receptor activator and prevention of cardiovascular events in hemodialysis patients—rationale and design of the Japan Dialysis Active Vitamin D (J-DAVID) trial

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## Abstract

**Background:** Activation of vitamin D is severely impaired in patients with advanced stages of chronic kidney disease, particularly those on hemodialysis. Observational studies have shown that the use of vitamin D receptor activators (VDRAs) is associated with lower risk of death from all-cause and cardiovascular disease (CVD) in dialysis populations regardless of serum parathyroid hormone (PTH) level. So far, however, there is no prospective trial to evaluate the effect of VDRAs administration on CVD prevention in hemodialysis patients.

**Methods:** The Japan Dialysis Active Vitamin D (J-DAVID) trial is a multi-center study with a prospective randomized open-label blinded endpoint (PROBE) design. The subjects are maintenance hemodialysis patients whose serum calcium is ≤10.0 mg/dL, phosphate is ≤6.0 mg/dL, and intact PTH is ≤180 pg/mL without taking any VDRA. The subjects (target number is 972) are randomized to one of the two treatment arms: treatment with oral alfacalcidol or treatment without using any VDRA and followed up for 48 months. The primary outcome is the composite of fatal and nonfatal cardiovascular events (myocardial infarction, heart failure requiring hospitalization, stroke, aortic dissection/rupture, amputation of lower limb due to ischemia, and cardiac sudden death, coronary revascularization, and leg artery revascularization). The secondary outcome is all-cause death. The primary analysis will be the intention-to-treat analysis of the primary endpoint.

**Results:** Between July 2008 and January 2011, a total of 976 participants were randomized. The final results are expected in the second half of 2016.

**Conclusions:** The J-DAVID trial will provide valuable information whether or not administration of VDRA reduces the risk of CVD in hemodialysis patients.

**Trial registration:** UMIN000001194

**Keywords:** Vitamin D, Vitamin D receptor activator (VDRA), Cardiovascular disease, Mortality, Chronic kidney disease (CKD), Hemodialysis, Clinical trial, CKD-MBD

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## Background

Hemodialysis patients are at an extremely elevated risk of death from all-cause and cardiovascular disease (CVD) in Western countries [1, 2] and in Japan [3] as well. The excess risk may be attributable to impairment in traditional [4] and nontraditional risk factors associated with chronic kidney disease (CKD) [1] such as insulin resistance [5], inflammation [6], protein-energy wasting [7], and CKD-mineral bone disorder (CKD-MBD) [8].

CKD-MBD is a systemic disorder in which abnormalities in phosphate and calcium metabolism are causatively involved not only in bone disease but also in vascular calcification and poor clinical outcomes in patients with CKD [8]. Patients with reduced kidney function show phosphate retention, increased fibroblast growth factor 23 (FGF23), impaired activation of 25-hydroxyvitamin D (25(OH)D) to 1,25-dihydroxyvatiamin D ($1,25(OH)_2D$), and secondary hyperparathyroidism [9]. Observational cohort studies have revealed the independent risk factors of mortality including elevated levels of serum phosphate, calcium, and intact parathyroid hormone (PTH) in hemodialysis patients in Western countries [10] and also in Japan [11, 12]. Furthermore, lower serum levels of 25(OH)D [13] and $1,25(OH)_2D$ [14] and higher FGF23 [15] levels are reported to be predictive of all-cause mortality in dialysis patients.

In addition to these abnormalities in laboratory tests, the use of medications for CKD-MBD is known to be associated with clinical outcomes of patients with CKD. The use of activated vitamin D sterols, or vitamin D receptor activators (VDRAs), was reported to be associated with lower risk of all-cause mortality [16–18], CVD-related mortality [19, 20], and incident CVD [21] in hemodialysis patients. Many, but not all [22], studies reported such associations as previously reviewed [23]. The hazard ratios of VDRA use versus no use for all-cause mortality were reported in the range between 0.55 and 0.75. In stratified analysis of a large cohort [16], the lower risk of mortality in VDRA users was significant regardless of serum levels of phosphate and calcium and intact PTH levels.

Although these observational studies suggest the potential benefit of VDRA, a controversy still exists on the overall benefit of treatment with VDRA in dialysis patients. Activation of VDR may increase the risk of CVD and mortality by increasing serum levels of calcium and phosphate, which could promote vascular calcification. Also, by increasing serum FGF23 production [24], a novel factor potentially promoting left ventricular hypertrophy [25] and a predictor of congestive heart failure (CHF) [26] and mortality [15], the use of VDRA may increase the risk of myocardial remodeling and CHF. On the contrary, VDRAs are shown to have potentially beneficial non-mineral actions [23] such as suppression of the renin-angiotensin system [27], modulation of immune functions [28], anti-inflammatory effects [29], and anti-atherosclerotic effects [30] on vascular cells. VDRA inhibits cardiac hypertrophy in experimental animals [31]. In addition, VDRA was reported to increase proteins potentially protective against arterial calcification [32, 33], including serum fetuin A [34] and klotho expressed in arterial wall [35]. Based on these findings, use of VDRA may suppress cardiac hypertrophy, atherosclerosis, arterial calcification, risk of CHF, atherosclerotic CVD, and mortality in patients with CKD. So far, however, no randomized controlled trials (RCTs) have been performed in hemodialysis patients to examine the possible effects of VDRA on risk of CVD or mortality.

We designed an RCT, the Japan Dialysis Active Vitamin D (J-DAVID) trial, to test a hypothesis that treatment with VDRA reduces the risk of CVD events in hemodialysis patients.

## Methods

### Study design

The J-DAVID trial is an RCT with a prospective randomized open-label blinded endpoint (PROBE) design. Eligible patients were randomly allocated to one of the two treatment arms: treatment with oral alfacalcidol (1α-hydroxycholecalciferol) or treatment without any VDRA. The follow-up period was 48 months (Fig. 1).

### Population

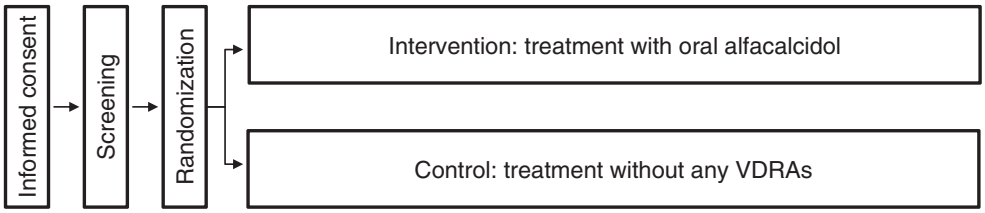
The target population of this study was maintenance hemodialysis patients whose serum calcium was ≤10.0 mg/dL, phosphate was ≤6.0 mg/dL, and intact PTH was ≤180 pg/mL without taking any VDRA at screening. These values derived from the 2006 version of the clinical practice guideline by the Japanese Society for Dialysis Therapy (JSDT) [36]. Eligibility criteria are shown in Table 1.

### Screening and enrollment

Eligible patients were screened at 207 study sites in 27 out of 47 prefectures in Japan (Fig. 2). The registration forms were sent by FAX to the Data Center at Osaka City University for registration and randomization. The registration codes and the assigned treatment groups were sent back by FAX to the attending physician within two working days.

### Randomization

Randomization was performed at a 1:1 ratio using a computer-generated random sequence with a block randomization method stratification by age (<65 years, ≥65 years), sex, years on dialysis (<5 years, ≥5 years), underlying renal disease (diabetic nephropathy, others), and prior CVD (with, without). Region of dialysis centers




| | IC | S | R | 0M | 3M | 6M | 12M | 18M | 24M | 30M | 36M | 42M | 48M |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed consent | X | | | | | | | | | | | | |
| Clinical background | | X | | X | | | | | | | | | |
| Laboratory data | | X | | X | X | X | X | X | X | X | X | X | X |
| Physical examination | | | | X | X | X | X | X | X | X | X | X | X |
| Use/nonuse of alfacalcidol | | X | | X | X | X | X | X | X | X | X | X | X |
| Other medications | | | | X | X | X | X | X | X | X | X | X | X |
| Primary & secondary outcomes, SAEs | | | | | X | X | X | X | X | X | X | X | X |

**Fig. 1** Design of the J-DAVID study. *IC* informed consent, *S* screening, *R* randomization, *M* months, *SAEs* serious adverse events

**Table 1** Eligibility criteria

Inclusion criteria

1. Signed informed consent
2. Patients on maintenance hemodialysis for 90 days or longer
3. Men or women aged ≥20 and ≤80 years old
4. No treatment with VDRAs for more than 4 weeks prior to this study
5. Serum calcium level ≤10.0 mg/dL
6. Serum phosphate level ≤6.0 mg/dL
7. Serum intact PTH level ≤180 pg/mL

Exclusion criteria

1. History within 12 weeks of myocardial infarction, stroke, aortic dissection/rupture, amputation of a lower limb, coronary revascularization or bypass surgery, lower limb revascularization or bypass surgery
2. Heart failure of NYHA grade III or IV
3. Respiratory failure with $PaO_2$ <60 mmHg or $SpO_2$ <90 %
4. Life expectancy shorter than 1 year due to known malignant, infectious, or other diseases
5. Abnormal liver function tests exceeding ×3 upper normal limits
6. Pregnant or lactating females or females planning to be pregnant
7. History of an allergic reaction to alfacalcidol
8. Participation to other interventional studies within 12 weeks prior to this study
9. Inappropriate for this study as judged by an attending investigator

*VDRAs* vitamin D receptor activators, *PTH* parathyroid hormone, *NYHA* New York Heart Association, $PaO_2$ arterial oxygen pressure, $SpO_2$ oxygen saturation measured by pulse oxymeter

was also considered in randomization because of possible regional disparities in life style, clinical practice patterns, and risk of CVD.

### Intervention and control treatment

The participants in the intervention arm were assigned to treatment with oral alfacalcidol at a starting dosage of 0.5 μg per day, which derived from our previous cohort study [19]. The participants in the control arm were assigned to treatment without any VDRA. Except VDRAs, all participants were eligible to receive any other medications for standard medical care including phosphate binders and cinacalcet.

### Follow-up

The clinical practice guidelines published by JSDT were the guide for treatment of CKD-MBD in hemodialysis patients. The 2006 version of the guideline [36] was initially used when the enrollment for J-DAVID was started in 2008. After its revision in 2012 [37], the revised version was used. Both versions of guideline recommended the same target ranges for serum phosphate and corrected calcium concentrations to be between 3.5 and 6.0 mg/dL and between 8.4 and 10.0 mg/dL, respectively. Regarding intact PTH level, the 2006 version suggested the target range between 60 and 180 pg/mL, whereas the 2012 version suggested the range between 60 and 240 pg/mL with a recommendation that control

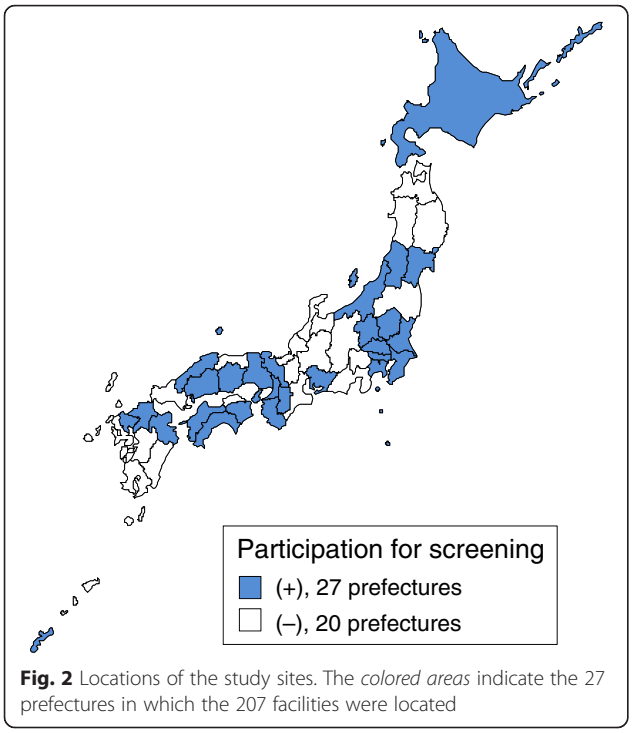



**Fig. 2** Locations of the study sites. The *colored areas* indicate the 27 prefectures in which the 207 facilities were located

of serum phosphorus and calcium levels be achieved prior to PTH.

The participants in the intervention arm were asked to avoid other VDRA preparations than oral alfacalcidol, but they were allowed to receive one if clinically needed. We defined the "drop-out" from the assigned treatment at the time when alfacalcidol was not taken continuously for more than 12 weeks in the intervention arm. The participants in the control arm were asked to avoid alfacalcidol and any preparations of VDRA, but they were allowed to receive one if clinically needed. The "drop-out" from the assigned treatment was defined at the time when treatment with any VDRA was done continuously for more than 12 weeks in the control arm. Participants who "dropped-out" from the assigned treatment were followed up until the end of the planned period for the intervention-to-treat (ITT) analysis.

### Outcomes and outcome adjudication

The primary outcome was defined as the composite of (1) fatal and nonfatal CVD events (acute myocardial infarction, congestive heart failure, stroke, aortic dissection/rupture, amputation of ischemic limb, and cardiac sudden death), (2) coronary intervention (plain old balloon angioplasty, stenting) or bypass grafting, (3) lower limb artery intervention (plain old balloon angioplasty, stenting) or bypass grafting. The definitions of the individual CVD events are listed in Table 2. The secondary outcome was defined as all-cause death. All these outcomes are being prospectively adjudicated by the Event Evaluation Committee with the assigned treatment of each case being masked to the Committee.

**Table 2** Definition of CVD events as parts of the primary outcome

| |
|---|
| Acute myocardial infarction: |
| Clinical signs and symptoms such as chest pain or cardiogenic shock, associated with abnormalities in biomarkers (creatine kinase, troponin, etc.) and/or electric cardiogram (new abnormal Q-wave, ST elevation, etc.) for myocardial infarction |
| Congestive heart failure: |
| Congestive heart failure (NYHA grade III or IV) requiring hospitalization, excluding dyspnea due to non-cardiac causes (bronchial asthma, etc.) |
| Stroke: |
| Rapidly developing clinical signs of neurological deficit attributable to a focal and/or total brain functions, without clear causes than vascular origin, lasting for more than 24 h or leading to death (if not interrupted by surgical operations or death). Stroke includes subarachnoidal hemorrhage, intracranial hemorrhage, and cerebral infarction but excludes transient ischemic attack, cerebrovascular disease due to hematological disorders (leukemia, polycytemia vera, etc.), primary brain tumors, and metastatic brain tumors. Stroke secondary to trauma is also excluded |
| Aortic dissection/rupture: |
| Clinical symptom of chest pain and/or abdominal pain, and diagnosed with imaging test such as contrast enhanced computed tomography |
| Amputation of ischemic limb: |
| Major amputations at ankle joint or proximal as treatment for patients with symptom and/or signs of lower extremity ischemia |
| Cardiac sudden death: |
| Unexpected death from a cardiac cause that occurs within one hour of symptom onset (witnessed) or within 24 h of last being observed in normal health (unwitnessed) |

### Safety

All serious adverse events (SAEs) and laboratory data are reported for safety. SAEs are defined as any undesirable experience during the study when the patient outcome is (1) death, (2) life-threatening, (3) hospitalization (initial or prolonged), (4) disability or permanent damage, (5) congenital anomaly/birth defect, or (6) other important medical events. SAEs are being prospectively adjudicated by the Event Evaluation Committee with the assigned treatment of each case being masked to the Committee. The laboratory data include serum intact PTH, calcium, phosphate, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and others.

### Source data verification

We planned to perform source data verification (SDV) by a sampling SDV. The minimum number of the extracted patients (31) was determined by $\sqrt{N}$, where $N = 976$. Sampling of participants was done by two steps using a computer-generated sequence. First, dialysis facilities were extracted, and then participants were sampled from the participants in the facility. In this study,

SDV was only performed regarding the primary and secondary outcomes.

### Study organization

The Steering Committee, which was lead by three academic investigators, nominated the members of the Executive Committee which promoted this study by organizing the research group (J-DAVID Research Group) comprised of dialysis facilities. Independent of the Steering Committee, the Executive Committee, and the J-DAVID Research Group, the J-DAVID study had the Data Center, the Event Evaluation Committee, the Statistics Team, the Independent Data Monitoring Committee, and the Audit Team. These contributors to the J-DAVID study are collectively called "J-DAVID Investigators" (Appendix).

### Statistical considerations

#### *Sample size and power calculation*

Assuming (1) that 28 % of participants in the control arm experience the primary outcome during the 4-year period, (2) that the risk is reduced by 30 % in the intervention arm, and (3) that 5 % of participants are lost to follow-up, the trial requires a minimum of 972 participants to detect difference in proportion of the primary endpoint between the two arms with 80 % power (ß level of 0.2) and α level of 0.05.

We assumed the rate of the primary outcome based on a cohort study of 45,390 prevalent Japanese hemodialysis patients without history of prior myocardial infarction or stroke at baseline [38]. The incidence rates of myocardial infarction, cerebral infarction, and cerebral bleeding during the 1-year follow-up (2004) were 1.43, 2.53, and 0.21 per 100 patient-year, respectively (4.17 in total) [38]. Some patients were expected to have avoided such clinical events by timely interventions. In addition, the incidence of these CVD events and interventions are expected to be much higher in patients with prior CVD than those without prior CVD. Thus, we assumed the rate of the primary outcome to be 7–9 % annually.

We assumed 30 % of the relative risk reduction based on previous observational cohort studies of prevalent hemodialysis patients. The hazard ratio of oral VDRA use versus nonuse for CVD mortality was reported to be 0.377 (95 % confidence interval 0.246–0.578) by a study from Japan [11] and 0.59 (95 % confidence interval 0.40–0.88) by a study in Latin American countries [20].

#### *Interim analysis*

Interim analysis was planned to be performed once by the Independent Data Monitoring Committee upon request by the Committee with a Haybittel-Peto method. On the interim analysis, 0.0001 of $\alpha$ is to be spent, and the final α is to be reduced to 0.0499 to maintain the study-wise $\alpha$ level of 0.05.

#### *Analysis plan*

We defined three populations for analysis: full analysis set (FAS), per-protocol set (PPS), and modified per-protocol set (modified PPS). (1) The FAS consists of all participants who were randomized and participants who "dropped-out" from the assigned treatment are not censored at the time of "drop-out." (2) The PPS consists of all participants who were randomized, but participants are censored at the time of "drop-out" from the assigned treatment. (3) The modified PPS consists of all participants who were randomized, and participants are censored as follows: In the control arm, participants are censored at the time of "drop-out" from the assigned treatment. In the intervention arm, participants who are censored at the time of "drop-out" from the assigned treatment with oral alfacalcidol, if no VDRA is given in place of alfacalcidol. Participants in the intervention arm are not censored at the time of "drop-out" from the assigned treatment with oral alfacalcidol, if the participants are kept treated with an oral or intravenous VDRA other than alfacalcidol, but such patients are censored at the time when any VDRA is not given continuously for more than 12 weeks.

The primary analysis will be performed using time after randomization to the occurrence of the primary composite outcome with the FAS based on the Kaplan-Meier method with log-rank test. Hazard ratio and confidence interval will be calculated with an unadjusted Cox proportional hazards model for the primary composite outcome and its breakdown. The key secondary analysis will be done with time after randomization to the secondary outcome (all-cause death) with the FAS based on the same methods as above. Additionally, the primary and secondary outcomes will be analyzed with the PPS and the modified PPS as sensitivity analysis.

## Results

### Participant recruitment and baseline characteristics

Recruitment of participants began in July 2008 and completed in January 2011. Eligibility was assessed in 1289 patients, and 976 patients from 108 dialysis facilities were enrolled and randomized. Table 3 gives the baseline characteristics of the total participants.

## Discussion

The J-DAVID study was originally designed to test a hypothesis that treatment with VDRA reduces the risk of CVD events as the primary endpoint and/or all-cause mortality as the secondary endpoint in hemodialysis patients. This hypothesis was based on the observational clinical studies and experimental studies reporting potential benefit of VDRAs.

**Table 3** Baseline characteristics of the participants

| | |
|---|---|
| Total number | 976 |
| Age (years) | 63.5 ± 10.0 |
| Sex, men (%) | 60.5 |
| Underlying renal disease, diabetic nephropathy (%) | 42.5 |
| Years on hemodialysis, 5 years or longer (%) | 52.2 |
| Prior cardiovascular disease, present (%) | 25.1 |
| Serum calcium (mg/dL) | 8.82 ± 0.60 |
| Serum phosphate (mg/dL) | 4.56 ± 0.91 |
| Serum intact parathyroid hormone (pg/mL) | 86.6 (46.8–130.0) |
| Use of calcium carbonate (%) | 82.9 |
| Use of sevelamer hydrochloride (%) | 32.0 |
| Use of lanthanum carbonate (%) | 12.4 |
| Use of cinacalcet hydrochloride (%) | 5.9 |

The table gives number, percentage, mean ± standard deviation, or median (25th–75th percentile)

After the enrollment for J-DAVID study was started in 2008, there have been two published RCTs regarding the use of VDRA and CVD in patients with CKD. The first one was the PRIMO study [39] and the second one was the OPERA study [40], both of which examined the effects of oral paricalcitol on left ventricular hypertrophy as determined by cardiac magnetic resonance imaging among predialysis patients with CKD. These two studies showed no significant effect of treatment with paricalcitol on the primary endpoint. Of note, however, CVD events were fewer in the paricalcitol group than the placebo group in the PRIMO study, and the number of hospitalization was fewer in the paricalcitol group than the placebo group in the OPERA study. These results are an additional support for the hypothesis of the J-DAVID study. So far, no RCT has been published that examined the VDRA's effect on CVD events or mortality in hemodialysis patients as well as in predialysis patients with CKD.

The use or nonuse of VDRA affects serum levels of phosphate, calcium, and intact PTH. Therefore, in order to maintain the key laboratory data within the target ranges, dietary therapy, and other medications would be changed over time after starting the assigned treatment. As compared with the participants in the control arm, the participants in the intervention arm may have higher levels of serum calcium and phosphate, and lower levels of intact PTH level on average, after starting the assigned treatment. More patients in the intervention arm may be treated with non-calcium-containing phosphate binders, whereas more patients in the control arm may be treated with cinacalcet. A meta-analysis showed a lower risk of death was associated with the use of non-calcium containing phosphate binders as compared with calcium containing phosphate binders in patients with CKD [41]. The same observation was made for either sevelamer hydrochloride [42] or lanthanum carbonate [43] in the elderly hemodialysis patients. Also, there is a discussion whether or not cinacalcet has cardio-protective actions [44]. Therefore, any effects on the primary and secondary endpoints in the J-DAVID study will not be purely attributable to the effect of alfacalcidol. Rather, this study would clarify whether the VDRA-based treatment is better than the treatment avoiding VDRA in terms of CVD prevention when other medications are available.

The current clinical practice guidelines for the management of CKD-MBD are largely based on observational cohort studies showing the associations of laboratory tests with all-cause mortality. However, the medications used for the control of the laboratory tests may be more important for clinical outcomes than the achieved serum levels of phosphate, calcium, and PTH. According to a recent meta-analysis [45], there are only weak and imprecise correlations of drug effects on serum levels of phosphate, calcium, and PTH with all-cause and cardiovascular death in patients with CKD, suggesting that the drug's non-mineral actions favorably affected these clinical endpoints. The same has been suggested also by previous cohort studies in which the use of VDRAs [16–21] or the use of phosphate-binders [21, 46] were associated with a lower risk of all-cause death, CVD death, or incident CVD in dialysis patients, even after adjusted for serum calcium, phosphate, and PTH levels. The J-DAVID study will reveal whether or not the VDRA treatment reduces CVD and/or mortality even when the current target ranges of phosphate, calcium, and intact PTH are respected.

## Conclusions

The J-DAVID study will be the first trial providing valuable information whether or not oral VDRA-based treatment reduces the risk of CVD and/or mortality in hemodialysis patients who are treated by respecting the recommended target ranges of serum phosphate, calcium, and intact PTH.

### Ethical approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki and the Ethical Guidelines for Clinical Research by the Ministry of Health, Labor and Welfare, Japan (July 30, 2003; December 28, 2004 all amendments; July 31, 2008 all amendments). The protocol of this study was first reviewed and approved by the Ethics Committee of Osaka City University Graduate School of Medicine, Osaka, Japan (No. 1227, 1297, 1385, and 1525), and by the Institutional Review Board/Ethics Committee at each study site. The study plan had been registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) before the first participant

was enrolled (UMIN-CTR Identifier: UMIN000001194). All participants gave informed consent before enrollment.

### Consent for publication
Not applicable.

### Availability of data and materials
No data is publicly available at present because data collection is still ongoing at the time of submission.

## Appendix
### Study organization "J-DAVID Investigators"
The following list indicates the contributors' names with institutions and prefectures in parenthesis:

#### *Steering Committee*
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**Principal investigator*

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#### *J-DAVID Research Group*
The following list indicates J-DAVID study sites by prefecture from which one or more participants were enrolled, excluding the institutions of the Executive Committee members:

*Aichi prefecture*—Kazuhiro Fujisawa (Kasugai Central Clinic), Sumie Tawada (Kojukai Kasugai Hospital), Satoshi Yamaguchi (Seto Kyoritsu Clinic)

*Chiba prefecture*—Yasuho Kimura (Shin Kashiwa Clinic)

*Fukushima prefecture*—Hirofumi Nakano (Kashima Hospital)

*Fukuoka prefecture*—Itsuko Ishida (Harasanshin Hospital Gofukumachi Jin Clinic), Tetsuo Komota (Komota Clinic), Dai Matsuo (Hirao Clinic), Hiroaki Takamura (Hara Hospital)

*Gunma prefecture*—Kyoko Ito (Heisei Hidaka Clinic)

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#### Abbreviations

$1,25(OH)_2D$: 1,25-dihydroxyvatiamin D; 25(OH)D: 25-hydroxyvitamin D; CKD: chronic kidney disease; CKD-MBD: chronic kidney disease-mineral bone disorder; CVD: cardiovascular disease; FAS: full analysis set; FGF23: fibroblast growth factor 23; ITT: intervention-to-treat; J-DAVID study: Japan Dialysis Active vitamin D study; JSDT: the Japanese Society for Dialysis Therapy; PPS: per-protocol set; PROBE: prospective randomized open-label blinded endpoint; PTH: parathyroid hormone; RCT: randomized controlled trial; SAEs: serious adverse events; SDV: source data verification; UMIN-CTR: University Hospital Medical Information Network Clinical Trials Registry; VDRA: vitamin D receptor activator.

#### Competing interests

T.S. received honorarium for lecturing and/or research grant from Asteras, Bayer, Boehringer Ingelheim, Chugai, Daiich Sankyo, Fuso, Kyowa Hakko Kirin (KHK), Mochida, MSD, Novo Nordisk, Pfizer, and Takeda Pharmaceutical. MI received research grant and/or honorarium for lecturing from Astellas, Bayer Yakuhin, Chugai, Daiichi Sankyo, Eli Lilly Japan, Kyowa Hakko Kirin, Mitsubishi Tanabe Pharma, MSD, Ono Pharmaceutical, Takeda Pharmaceutical, and Teijin Parma. Y.N. received honorarium for lecturing from Chugai, Kyowa Hakko Kirin, and Ono Pharmaceutical.

#### Authors' contributions

As the Steering Committee members, TS, MI, and YN contributed to the concept and design of the study, to organizing the study group, and to manuscript writing. All authors read and approved the final manuscript.

#### Acknowledgements

The study design was presented as a poster (SA-PO2619) at the Kidney Week 2011 of the American Society of Nephrology (Philadelphia (PA)) and published as an abstract (J Am Soc Nephrol 22: 721A, 2011). The J-DAVID study was supported by many clinical research coordinators from the following site management organizations: Clinical Support Corporation (Tokyo), EP-Mint Co., Ltd. (Aichi), I'ROM Co., Ltd. (Tokyo), Medical Toyou Co., Ltd. (Kanagawa), Site Support Institute Co., Ltd. (Tokyo), Souken Co., Ltd. (Tokyo).

#### Funding

The J-DAVID study was funded by the grant from The Kidney Foundation, Japan.

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Received: 31 January 2016 Accepted: 29 February 2016
Published online: 25 April 2016

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