Supplementary Online Content

The J-David Investigators. Prospective, randomized, open-label, blinded-endpoint trial to examine the effect of active vitamin D on cardiovascular events in hemodialysis patients: Japan Dialysis Active Vitamin D trial (J-DAVID). JAMA. doi:10.1001/jama.2018.17749

Supplement 2. Statistical analysis plan

This supplementary material has been provided by the authors to give readers additional information about their work.

Statistical Analysis Plan for J-DAVID Trial

Version 1 Jan 29, 2016

Version 2 Dec 10, 2016

1. Introduction

This statistical analysis plan describes in detail the statistical methods which were outlined in the version 2.6 protocol of "Prospective, randomized, open-label, blinded-endpoint trial to examine the effect of active vitamin D on cardiovascular events in hemodialysis patients: Japan Dialysis Active Vitamin D trial (J-DAVID)", "10. Handling of cases and statistical analysis".

2. Outline of the J-DAVID trial

(1) The purpose of this study

The purpose of this study is to examine whether active vitamin D reduces the risk of cardiovascular events in hemodialysis patients in a randomized clinical trial ("3. Purpose and outcome measures" in the Protocol).

(2) The design of this study

- This study is a prospective, randomized, open-label, blinded-endpoint (PROBE) trial. The target participant number of this multicenter study is 972, 486 for each arm, and the follow-up period is 4 years (3, 6, 12, 18, 24, 30, 36, 42, and 48 months) for each participant.
- The day of randomization shall be defined as day 0, and the end of follow-up after 48 months shall be defined as the same day of the same month after 4 years.

3. Populations for analysis

(1) Definitions

We define three populations for analysis: full analysis set (FAS), per-protocol set (PPS), and modified per-protocol set (modified PPS) as follows;

- The FAS shall consist of all participants who were randomized and participants who "dropped-out" from the assigned treatment shall not be censored at the time of "drop-out."
- The PPS shall consist of all participants who were randomized, but participants shall be censored at the time of "drop-out" from the assigned treatment.
- The modified PPS shall consist of all participants who were randomized, and participants shall be censored as follows: In the control arm, participants shall be censored at the time of "drop-out" from the assigned treatment. In the intervention arm, participants shall be 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 shall not be

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 shall be censored at the time when any VDRA is not given continuously for more than 12 weeks.

(2) Handling of participants

- Regarding participants who discontinued the participation to this study after randomization, they shall be censored at the time of discontinuation. In such cases, if the day of discontinuation is just after randomization but not clearly reported, the participant shall be censored on the next day after randomization.
- Regarding participants who experienced the primary or secondary outcome just after randomization but the date was not specifically reported, we shall handle the day of the outcome to be the next day after randomization.
- Regarding participants who were found not to meet the eligibility criteria after randomization, such participants shall be excluded from all the populations for analysis.

4. Items and methods for analysis

(1) Clinical characteristics of the participants

For summary data of the clinical characteristics of the participants, categorical data shall be shown as number (percentage) of participants and continuous variables shall be shown as median (IQR), by the treatment groups. No test shall be done to compare between the groups. The baseline data shall be based on the case report form (CRF) "before starting assigned treatment" and include the following items;

A) Clinical background: age, sex, years on hemodialysis, underlying renal disease, past history of cardiovascular disease, past history of parathyroid intervention (parathyroidectomy, percutaneous ethanol injection therapy, etc.), hemodialysis conditions (dialysis hours per week, Kt/V, dialysate Ca concentration)

B) Laboratory data: Complete blood count (WBC, RBC, Hb, Ht, Platelet), serum biochemistry (P, Ca, intact PTH, albumin, AST, ALT, ALP, BUN, Cr, Na, K, Cl, TC, TG, HDL-C, Non-HDL-C). Only in participants with diabetes mellitus, HbA1c (NGSP: If HbA1c is reported by JDS-value, convert it to NGSP value by adding 0.4), Glycoalbumin (GA). Corrected calcium shall be calculated by the equation: corrected calcium (mg/dL) = Ca + (4–serum albumin), if serum albumin is lower than 4.0 g/dL. Corrected calcium = Ca, if serum albumin is 4.0 or higher. If serum albumin is missing, corrected calcium = Ca. Non-HDL-C shall be calculated as TC minus HDL-C.

C) Physical examination: height, body weight (dry weight), BMI, blood pressure (SBP, DBP), and pulse rate. BMI shall be calculated as body weight (kg) divided by square of height (m).

D) Medications: Use or non-use of the nine categories of drugs documented in the CRF: Category 1, Drugs for CKD-MBD (calcium carbonate, sevelamer hydrochloride, cinacalcet hydrochloride, lanthanum carbonate, intravenous VDRA, others); Category 2, Antihypertensives (calcium channel blocker, ACE inhibitor, ARB, beta-blocker, loop diuretics, others); Category 3, Other cardiovascular drugs (digitalis, anti-arrhythmic, coronary artery dilator, others); Category 4, Anti-platelet agents (asprin, ticlopidine hydrochloride, cilostazol, others); Category 6, Anti-diabetic agents (insulin injection, sulfonyl urea, rapid acting insulin secretagogue, alfa-glucosidase inhibitor, others); Category 7, lipid-lowering agents (statin); Category 8, ESAs (human recombinant erythropoietin, long-acting ESA); Category 9, iron preparations

(oral, intravenous). In addition to the individual counts within the category, aggregated counts shall also be done in Category 1 and Category 6. Regarding Category 1, the use of 'Any phosphate binders' shall be any use of calcium carbonate, sevelamer hydrochloride, cinacalcet hydrochloride, or lanthanum carbonate. Regarding Category 6, the use of 'Any oral anti-diabetic agents' shall be any use of sulfonyl urea, rapid acting insulin secretagogue, α-glucosidase inhibitor, or others. Regarding Category 9, counts shall also be done for the use of oral iron and intravenous preparations individually.

(2) Analysis of treatment status and adherence

For the following analyses, the population for analysis shall be the FAS including all participants who survived to a certain time point regardless of the occurrence of the primary outcome. The analyses shall be based on the data of CRFs at the predefined time points (Before starting assigned treatment, 3M, 6M, 12M, 18M, 24M, 30, 36M, 42M, and 48M) and the data of the "Compliance Sheet for alfacalcidol", and calculated by group.

- Number and proportion of the users of phosphate binders, cinacalcet, and intravenous VDRA at the predefined time points.
- Median values of serum corrected calcium, phosphate, and intact PTH at the predefined time points. The numbers of analyzed participants shall be indicated for possible missing data.
- Adherence to the assigned treatment
- Mean daily dose of alfacalcidol

Adherence to the assigned treatment shall be based on the definition of 'drop-out' from the assigned treatment. In the intervention group, we define the 'drop-out' from the assigned treatment at the time when alfacalcidol is not taken continuously for more than 12 weeks in the intervention group. In the control group, the 'drop-out' from the assigned treatment is defined at the time when treatment with any VDRA is done continuously for more than 12 weeks. The adherence to the assigned treatment is calculated with the data from the 'Compliance Sheet for alfacalcidol'. The proportions of participants who adhere to the assigned treatment by the two groups shall be drawn by the Kaplan-Meier method. Mean daily dose of alfacalcidol shall be calculated by the total dose of alfacalcidol divided by the days of observation.

(3) Primary outcome

- The primary outcome is defined as the composite of 1) fatal and nonfatal cardiovascular events including acute myocardial infarction, congestive heart failure requiring hospitalization, 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.
- We use the time (days) to the primary outcome since randomization for analysis. In the cases with multiple events that fall into the primary outcome, the time to the first event after randomization shall be analyzed.
- The primary analysis shall be the ITT analysis with the FAS. The event-free survival curves shall be constructed by the Kaplan-Meier method, and evaluated by the log-rank test. Hazard ratios (95% confidence intervals) shall

be calculated with unadjusted Cox proportional hazard model for the composite primary outcome and its breakdown.

(4) Secondary outcome

The secondary outcome is all-cause death. The key secondary analysis is the ITT analysis with the FAS. Survival curves shall be constructed by the Kaplan-Meier method, and evaluated by the log-rank test. Hazard ratio (95% confidence interval) shall be calculated with unadjusted Cox proportional hazard model.

(5) Additional analysis of the primary and secondary outcomes

In addition to the above mentioned analyses, we shall perform analyses of the primary and secondary outcomes using the PPS and modified PPS. Also, the primary analysis and the key secondary analysis shall be further adjusted for age, sex, dialysis duration, diabetic nephropathy or not, and the presence of prior cardiovascular disease using multivariate Cox proportional hazard model.

(6) Safety analysis (Adverse events)

Safety shall be analyzed with the FAS. We shall calculate 1) the number of all serious adverse events (SAEs) after randomization by group, and 2) the numbers (percentages) of abnormalities by group in the predefined laboratory items at the predefined time points.

1) SAEs: SAEs shall include the primary and secondary outcomes. Total SAEs shall be categorized into cardiovascular, infection, malignancy, falls/bone fracture, accidents, and others.

2) Laboratory abnormalities: We shall base on the CRFs of the predefined time points (Before starting assigned treatment, 3M, 6M, 12M, 18M, 24M, 30, 36M, 42M, and 48M). The predefined laboratory abnormalities are; corrected calcium > 10.0 mg/dL, phosphate > 6.0 mg/dL, intact PTH > 240 pg/mL, corrected calcium > 11.0 mg/dL, phosphate > 7.0 mg/dL, and intact PTH > 500 pg/mL.

(7) Units and digit numbers

The table below indicates the units and digital numbers of numerical data;

Item	Unit	Number of decimal places
Dialysis hours per session (entered by 0.5 hr interval)	hour	1
Dialysate calcium concentration	mEq/L	2
Single pool Kt/V*	-	2
WBC	/μL	0
RBC	10^6/μL	0
Hb	g/dL	1
Ht	%	1
Platelet	10^4/μL	1
P	mg/dL	1

Ca	mg/dL	1
Intact PTH	pg/mL	0
Albumin	g/dL	1
CRP	mg/dL	2
AST	IU/L	0
ALT	IU/L	0
ALP	IU/L	0
BUN	mg/dL	0
Cr	mg/dL	1
Na	mEq/L	0
K	mEq/L	1
Cl	mEq/L	0
TC	mg/dL	0
TG	mg/dL	0
HDL-C	mg/dL	1
Non-HDL-C**	mg/dL	0
HbA1c	%	1
GA (Glycoalbumin)	%	1
Height	cm	0
Body weignt (dry weight)	kg	1
BMI***	kg/m^2	1

* Kt/V is calculated by the following formula;

$$Kt/V = -LN\left(\frac{\text{BUN after HD}}{\text{BUN before HD}} - 0.008\times\text{length of HD in hours}\right) + \left(4 - 3.5 \times \frac{\text{BUN after HD}}{\text{BUN before HD}}\right) \times \frac{\text{Body weigh before HD} - \text{Body weight after HD}}{\text{Body weight before dialysis}}$$

** Non-HDL-C shall be calculated by the formula: Non-HDL-C ＝ TC – HDL-C

***BMI is defined by the formula: BMI = Dry weight (kg) divided by [height (m)]^2

(8) Missing data

No imputation shall be done for missing data using calculation or estimation.

(9) Level of significance and confidence interval

Level of significance 5% (two-sided)

Confidence interval 95% (two-sided)

5. Schedule of data collection and analysis

- We calculate data for the baseline characteristics after completion of the registration of the participants and the

fixation of data from the CRF (Before starting the assigned treatment).

- Interim analysis is planned to be performed once by the Independent Data Monitoring Committee, if the Committee decided to perform it after interim data review. The method of interim analysis shall be described in the interim analysis plan.
- The final analyses shall be performed after all data are fixed.

6. Storage and management of data and documents

Data set for analysis, results of analysis, and related data documents shall be stored so that the dates of records are identifiable. The storage periods shall be 5 years for paper-based data/documents and 10 years for electronic data/documents after publication as a research paper.

The modifications from version 1 to version 2 are indicated in red

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