

# BPB Reports

## Report

### Comparison of Predictive Performance of Drug Dose Settings Using Renal Function Estimation Equations Based on the Japanese Population: A Preliminary Retrospective Study Using Vancomycin Dosing Data

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The Cockcroft–Gault (C–G) equation is widely used for drug dose settings in Japan. However, several reports have questioned its accuracy. In previous decades, estimation equations of creatinine clearance (CCr), such as the Orita–Horio equation, have been established based on the Japanese population. We previously built the fitted C–G and fitted Orita–Horio equations by fitting the coefficients of the estimation equations to the study population. However, the usefulness of these equations for drug dose settings remains unclear. Our preliminary study verifies the accuracy of these equations by comparing the predictive performance of the initial vancomycin (VCM) trough value between four equations: the conventional C–G (as control), conventional Orita–Horio, fitted C–G, and fitted Orita–Horio equations. Patients receiving VCM intravenously between January 2015 and March 2019 at Hokkaido University Hospital were enrolled. Overall, 308 patients were included. As initial dose setting methods, we selected two therapeutic drug monitoring (TDM) analysis software: SHIONO-GI-VCM-TDM ver.2009 (VCM-TDM) and Vancomycin MEEK TDM analysis software Ver2.0 (MEEK). Predictive performances were evaluated by calculating mean prediction error and mean absolute prediction error (MAE). The lowest MAE was obtained with the conventional C–G equation using VCM-TDM, indicating high predictive performance. However, contrasting result was obtained with MEEK, where the highest MAE was obtained using conventional C–G equation. Moreover, no significant differences were observed in MAE between the other three equations, suggesting that accurate dose settings are not always achieved, despite using accurate CCr equations based on the Japanese population.

**Key words** creatinine clearance, renal function, drug dose settings, vancomycin

## INTRODUCTION

Accurate evaluation of renal function is important for dose settings of renal excretion-type drugs. The Cockcroft–Gault (C–G) equation for the estimation of creatinine clearance (CCr), established based on the data of 249 Western patients,<sup>1)</sup> is widely used for determining drug dose settings in Japan.<sup>2,3)</sup> Using this equation, users can estimate the CCr quickly and easily. However, several reports have questioned the accuracy of using the C–G equation. It has been reported that the C–G equation tends to deviate from the actual values measured in elderly individuals.<sup>4–6)</sup> In addition, this equation has a risk of overestimating drug doses in obese patients from the use of real body weight.<sup>7,8)</sup>

Over several decades, equations for estimation of CCr, such as the Orita–Horio equation, were established based on Japanese patient data.<sup>9)</sup> The Orita–Horio equation has succeeded in improving the predictive accuracy of CCr compared with the conventional C–G equation. In our previous study, we evaluated these equations by comparing measured CCr data.<sup>10)</sup> Moreover, we successfully developed the fitted C–G and fitted

Orita–Horio equations by fitting the coefficients of the estimation equations to the study population, taking into particular consideration elderly patients.<sup>10)</sup> However, the usefulness of these CCr estimation equations for drug dose settings remains unclear.

Intravenously administered vancomycin (VCM) is one of the renal excretion-type antibiotics and is the first-line therapy for methicillin-resistant *Staphylococcus aureus* infections.<sup>11)</sup> As a preliminary study, we selected this antibiotic for validating the accuracy of drug dose settings of four CCr estimation equations: conventional C–G,<sup>1)</sup> conventional Orita–Horio,<sup>9)</sup> fitted C–G, and fitted Orita–Horio equations.<sup>10)</sup> One of the advantages of using VCM for this study is that patients treated with this agent routinely require therapeutic drug monitoring (TDM), meaning that the serum trough value can be obtained easily.<sup>11,12)</sup> Moreover, approximately 200 patients received VCM within one year at the Hokkaido University Hospital,<sup>13)</sup> and initial dose settings were also determined by pharmacists based on CCr calculated using the conventional C–G equation.<sup>14)</sup> At our hospital, we employ the TDM analysis software for determining the initial dose settings of VCM, constructed

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using pharmacokinetic (PPK) parameters of the Japanese population.<sup>14,15</sup> The target trough level of VCM was set to 10–20 mg/L based on several guidelines.<sup>11,12,14</sup>

In our previous study, we compared the predictive performance of two TDM analysis software, namely “SHIONOGI-VCM-TDM ver.2009 (VCM-TDM)” and “Vancomycin MEEK TDM analysis software Ver2.0 (MEEK).”<sup>16</sup> We determined that VCM-TDM showed a higher predictive performance than MEEK; as a result, VCM-TDM is employed at our hospital.<sup>14,16</sup> Thus, it is essential to verify whether the prediction performance changes if the CCr estimation equations that are constructed or fitted based on Japanese patients are inserted into these TDM analysis software.

In this study, our objective was to validate the usefulness of CCr estimation equations that were constructed or fitted based on Japanese parameters for determining dose settings of renal excretion-type drugs. Specifically, we compared the predictive performance of initial VCM trough values among conventional C–G (used as a control), conventional Orita–Horio, fitted C–G, and fitted Orita–Horio equations using two TDM analysis software.

## MATERIALS AND METHODS

**Patients** All data were obtained retrospectively from the patients’ medical records at Hokkaido University Hospital. Patients who had received VCM intravenously from January 2015 to March 2019 were included in our study if they (1) were aged  $\geq 18$  years, (2) had a VCM trough value at the steady state, and (3) had their initial VCM dose settings determined by pharmacists. Patients were excluded if they (1) received VCM therapy  $< 3$  days, (2) received initial VCM loading dose, (3) received renal replacement therapy, such as hemodialysis and continuous hemodiafiltration, or (4) had nephrotoxicity before the VCM trough value was measured. The steady state was defined as the duration from the beginning of administration to when the initial TDM was more than 4 half-lives of VCM.<sup>17</sup> Half-lives were calculated individually based on the Japanese PPK parameters reported by Yasuhara *et al.*<sup>15</sup> At our hospital, as described above, initial dose settings were performed using the TDM analysis software VCM-TDM.<sup>14,15</sup> In addition, nephrotoxicity was assessed if the serum creatinine (Scr) level increased to at least 0.5 mg/dL or 50% or higher from the baseline.<sup>11</sup>

**Outcomes** The primary endpoint was to assess the predictive performance of the initial VCM trough value of the CCr estimation equations: the conventional C–G (as control), conventional Orita–Horio, fitted C–G, and fitted Orita–Horio equations. The latter three equations were constructed or fitted based on Japanese data.<sup>9,10</sup> As initial dose setting methods, we selected two TDM analysis software that incorporate Japanese PPK parameters<sup>15,18</sup>: “VCM-TDM” and “MEEK.” We evaluated predictive performances by calculating the mean prediction error (ME) and mean absolute prediction error (MAE) as follows<sup>19</sup>:

$$ME (\%) = \frac{1}{n} \sum_{i=1}^n \left[ \frac{\text{predicted trough value} - \text{actual trough value}}{\text{actual trough value}} \times 100 \right],$$

$$MAE (\%) = \frac{1}{n} \sum_{i=1}^n \left[ \frac{|\text{predicted trough value} - \text{actual trough value}|}{\text{actual trough value}} \times 100 \right].$$

As a secondary endpoint, we evaluated ME and MAE by dividing patients into subgroups based on their gender, CCr,

and age. CCr was calculated using the conventional C–G equation and classified as  $CCr \geq 85$  mL/min or  $< 85$  mL/min.<sup>16</sup> Age was classified as generation I (20–39 years), generation II (40–64 years), generation III (65–74 years), and generation IV (over 75 years).<sup>10</sup>

**Renal Function Estimation Equations** Estimation equations of renal function were evaluated as follows: IBW, ABW, TBW, and BMI indicate ideal body weight, adjusted body weight, total body weight, and body mass index, respectively.

### ➤ Cockcroft–Gault (C–G) equation<sup>1</sup>

$$\text{Men: } CCr (\text{mL/min}) = \frac{(140 - \text{Age}) \times \text{ABW} (\text{kg})}{72 \times \text{Scr} (\text{mg/dL})}$$

$$\text{Women: } CCr (\text{mL/min}) = \frac{(140 - \text{Age}) \times \text{ABW} (\text{kg})}{72 \times \text{Scr} (\text{mg/dL})} \times 0.85$$

### ➤ Orita–Horio equation<sup>9</sup>

$$\text{Men: } CCr (\text{mL/min}) = \frac{(33 - 0.065 \times \text{Age} - 0.493 \times \text{BMI}) \times \text{TBW} (\text{kg})}{\text{Scr} (\text{mg/dL}) \times 14.4}$$

$$\text{Women: } CCr (\text{mL/min}) = \frac{(21 - 0.030 \times \text{Age} - 0.216 \times \text{BMI}) \times \text{TBW} (\text{kg})}{\text{Scr} (\text{mg/dL}) \times 14.4}$$

### ➤ Fitted C–G equation<sup>10</sup>

$$\text{Men: } CCr (\text{mL/min}) = \frac{(160 - \text{Age}) \times \text{ABW} (\text{kg})}{72 \times \text{Scr} (\text{mg/dL})}$$

$$\text{Women: } CCr (\text{mL/min}) = \frac{(160 - \text{Age}) \times \text{ABW} (\text{kg})}{72 \times \text{Scr} (\text{mg/dL})} \times 0.96$$

### ➤ Fitted Orita–Horio equation<sup>10</sup>

$$\text{Men: } CCr (\text{mL/min}) = \frac{(38 - 0.112 \times \text{Age} - 0.509 \times \text{BMI}) \times \text{TBW} (\text{kg})}{14.4 \times \text{Scr} (\text{mg/dL})}$$

$$\text{Women: } CCr (\text{mL/min}) = \frac{(32 - 0.086 \times \text{Age} - 0.418 \times \text{BMI}) \times \text{TBW} (\text{kg})}{14.4 \times \text{Scr} (\text{mg/dL})}$$

For calculating the C–G and fitted C–G equations, body weight was adjusted based on the degree of obesity, defined as “[TBW – IBW]  $\times$  100/IBW (%)”.<sup>10</sup> If the degree of obesity was between 30% and 100%, IBW was used for CCr calculations. When the degree of obesity was more than 100%, ABW was employed. Equations of IBW and ABW were as follows:

$$IBW (\text{Men}) = 50 + 2.3 \times \frac{\text{Height} (\text{cm}) - 150}{2.5}$$

$$IBW (\text{Women}) = 45 + 2.3 \times \frac{\text{Height} (\text{cm}) - 150}{2.5}$$

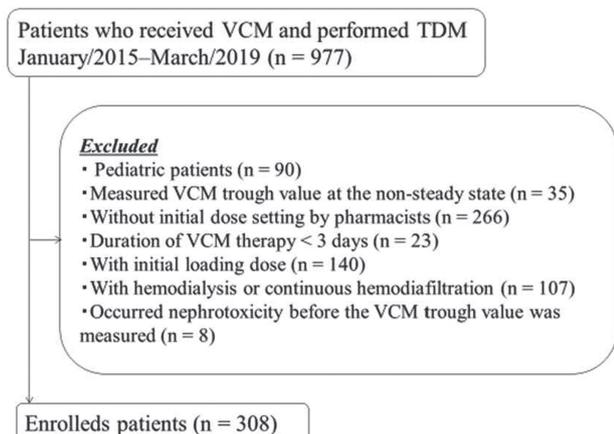
$$ABW = IBW + 0.4 \times (\text{TBW} - \text{IBW})$$

For calculation of the Orita–Horio and fitted Orita–Horio equations, body weight was not adjusted because BMI is already incorporated as a parameter in these equations.

**Data Collection** We collected data for age, gender, body weight, BMI, Scr, duration of VCM therapy, duration in the intensive care unit, initial VCM trough value, and days to initial TDM. All data were evaluated at the beginning of VCM administration, except for duration of VCM therapy, initial VCM trough value, and days to initial TDM.

**Statistical Analysis** For comparison of MAE and ME among the four groups (i.e., conventional C–G, conventional Orita–Horio, fitted C–G, and fitted Orita–Horio equations), Bonferroni multiple comparison test was performed.  $P \leq 0.05$  was defined as statistically significant.

All statistical analyses were performed using SPSS statis-



VCM: vancomycin; TDM: therapeutic drug monitoring

Fig. 1. Study Inclusion and Exclusion Flowchart

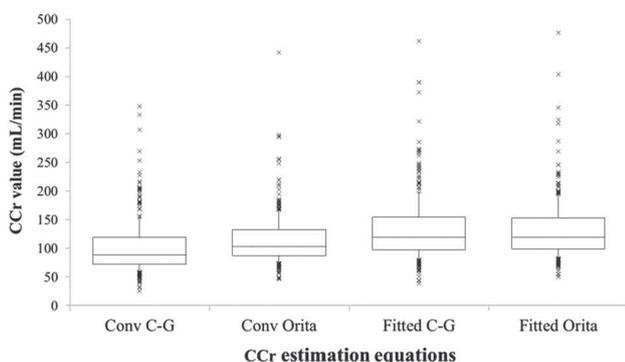


Fig. 2. Distribution of CCr Values Calculated Using Each CCr Estimation Equation

Each box plot shows the distribution of creatinine clearance. Each box shows: upper horizontal line of box, 75th percentile; lower horizontal line of box, 25th percentile; horizontal bar within box, median; upper horizontal bar outside box, 90th percentile; lower horizontal bar outside box, 10th percentile. CCr: creatinine clearance, Conv: conventional, C-G: Cockcroft–Gault equation, Orita: Orita–Horio equation.

tics 25 (IBM, Tokyo, Japan).

**Ethics** This study was performed in accordance with the guidelines for the care for humans. The ethics committee of Hokkaido University Hospital approved our protocol (NO. 019-0038).

## RESULTS

**Characteristics of patients** Of the 977 initial patients, 308 were included in the study (Fig. 1). Patient characteristics are shown in Table 1. The average CCr estimated by each equation was as follows: conventional C–G,  $102.0 \pm 46.9$  (mean  $\pm$  standard deviation) mL/min; conventional Orita–Horio,  $115.0 \pm 44.3$  mL/min; fitted C–G,  $132.7 \pm 57.2$  mL/min; and fitted Orita–Horio,  $130.9 \pm 51.6$  mL/min. The distribution of CCr estimated by each equation is shown in the box plot in Fig. 2. The average initial VCM trough value was  $11.6 \pm 4.93$  mg/L.

**Comparison of Predictive Performance of Initial VCM Trough Value of Each CCr Estimation Equation** Table 2 shows the predictive performances of each CCr estimation

Table 1. Patient Characteristics

Descriptions	Eligible patients (n = 308)
Age (years)	60.5 $\pm$ 15.2 (20–96)
Generation I (age: 20–39 years)	35 (11.4)
Generation II (age: 40–64 years)	130 (42.2)
Generation III (age: 65–74 years)	97 (31.5)
Generation IV (age: 75–years)	46 (14.9)
Gender (male), n (%)	198 (64.3)
Body weight (kg)	58.7 $\pm$ 11.7 (33.5–107.7)
Body mass index	22.1 $\pm$ 3.81 (14.0–40.6)
Serum creatinine (mg/dL)	0.65 $\pm$ 0.21 (0.16–1.58)
Creatinine clearance (mL/min)	
Conventional Cockcroft–Gault equation	102.0 $\pm$ 46.9 (26.0–348.1)
Conventional Orita–Horio equation	115.0 $\pm$ 44.3 (46.4–442.0)
Fitted Cockcroft–Gault equation	132.7 $\pm$ 57.2 (39.4–461.9)
Fitted Orita–Horio equation	130.9 $\pm$ 51.6 (50.8–476.6)
Duration of VCM therapy (days)	11.5 $\pm$ 8.7 (3–61)
Residence in intensive care unit	35 (11.4)
Duration of initial TDM (days)	3.80 $\pm$ 0.81 (3–7)
Initial VCM daily dose (mg)	1894.2 $\pm$ 499.0 (750–3750)
Initial VCM trough value (mg/L)	11.6 $\pm$ 4.93 (2.4–36.0)

Continuous variables: mean  $\pm$  standard deviation (range), categorical variables: n (%), TDM: therapeutic drug monitoring, VCM: vancomycin.

equation using VCM-TDM. As for the ME, the conventional C–G equation was found to be significantly the closest to 0 points in all subgroups, except for generation I patients and patients with CCr  $\geq 85$  mL/min. This implies that the prediction bias was lower with the conventional C–G equation than with other equations, although they were all constructed or fitted based on Japanese data. In addition, the lowest value of MAE was obtained using the conventional C–G equation except for female patients, generation I and II, and patients with CCr  $\geq 85$  mL/min and  $< 85$  mL/min, indicating high predictive performance.

As shown in Table 3, the opposite results were obtained using the TDM analysis software “MEEK.” The ME and MAE values obtained using the conventional C–G equation were significantly higher than when other equations were used, except in the case of generation I patients, patients with CCr  $\geq 85$  mL/min and  $< 85$  mL/min. Additionally, there were no significant differences in MAE among the other three equations in all the groups. A positive ME indicates that the predicted trough value is higher than the actual trough value, and therefore, the equation has a risk of underestimating the VCM dose, indicating low predictive accuracy.

## DISCUSSION

Previous studies indicated that the predictive accuracies of CCr were improved using conventional Orita–Horio, fitted C–G, and fitted Orita–Horio equations that were constructed or fitted based on data obtained from the Japanese population.<sup>9,10</sup> However, it is unknown whether these CCr estimation equations are useful for accurately predicting drug dose settings. As a preliminary study, we evaluated the predictive performances of these equations using VCM dosing data.

In the index of predictive performances, ME indicates prediction bias because a positive ME indicates that the predicted trough value is higher than the actual value. MAE measures

**Table 2.** Predictive Performance of Initial VCM Trough Value of Each CCr Estimation Equation Using TDM Analysis Software VCM-TDM

	ME ± SD				MAE ± SD			
	Conv C-G	Conv Orita	Fitted C-G	Fitted Orita	Conv C-G	Conv Orita	Fitted C-G	Fitted Orita
All patients (n = 308)	-1.56 ± 5.00 <sup>*,†,‡</sup>	-3.65 ± 4.77 <sup>†,‡</sup>	-5.04 ± 4.60	-5.10 ± 4.62	3.79 ± 3.62 <sup>*,†,‡</sup>	4.49 ± 3.98 <sup>†,‡</sup>	5.31 ± 4.29	5.39 ± 4.27
Male (n = 198)	-1.85 ± 4.84 <sup>*,†,‡</sup>	-3.90 ± 4.65 <sup>†,‡</sup>	-4.85 ± 4.50	-5.02 ± 4.54	3.75 ± 3.57 <sup>*,†,‡</sup>	4.53 ± 4.04 <sup>†,‡</sup>	5.08 ± 4.24	5.28 ± 4.24
Female (n = 110)	-1.04 ± 5.27 <sup>*,†,‡</sup>	-3.18 ± 4.96 <sup>†,‡</sup>	-5.39 ± 4.78	-5.24 ± 4.76	3.84 ± 3.73 <sup>†,‡</sup>	4.41 ± 3.89 <sup>†,‡</sup>	5.72 ± 4.37	5.58 ± 4.35
CCr ≥ 85 mL/min (n = 171)	-2.93 ± 4.88 <sup>†,‡</sup>	-3.73 ± 4.96 <sup>†</sup>	-5.52 ± 4.71	-5.11 ± 4.80	3.97 ± 4.07 <sup>†,‡</sup>	4.49 ± 4.27	5.63 ± 4.57	5.33 ± 4.55
CCr < 85 mL/min (n = 137)	0.15 ± 4.63 <sup>*,†,‡</sup>	-3.55 ± 4.53 <sup>‡</sup>	-4.45 ± 4.41	-5.08 ± 4.40	3.55 ± 2.96 <sup>†,‡</sup>	4.49 ± 3.59	4.91 ± 3.89	5.46 ± 3.91
Generation I (age: 20–39 years) (n = 35)	-3.75 ± 4.06 <sup>*,†,‡</sup>	-3.06 ± 4.13 <sup>†,‡</sup>	-5.51 ± 4.10 <sup>‡</sup>	-4.82 ± 4.11	4.11 ± 3.69 <sup>†,‡</sup>	3.76 ± 3.48 <sup>†,‡</sup>	5.51 ± 4.09	4.96 ± 3.93
Generation II (age: 40–64 years) (n = 130)	-1.89 ± 5.72 <sup>*,†,‡</sup>	-3.16 ± 5.47 <sup>†,‡</sup>	-5.24 ± 5.38	-4.90 ± 5.29	4.20 ± 4.30 <sup>†,‡</sup>	4.47 ± 4.45 <sup>†,‡</sup>	5.62 ± 4.98	5.37 ± 4.81
Generation III (age: 65–74 years) (n = 97)	-0.96 ± 4.23 <sup>*,†,‡</sup>	-4.09 ± 4.30 <sup>†,‡</sup>	-4.86 ± 3.96 <sup>‡</sup>	-5.30 ± 4.16	3.31 ± 2.78 <sup>*,†,‡</sup>	4.61 ± 3.73 <sup>‡</sup>	5.06 ± 3.69	5.47 ± 3.93
Generation IV (age: 75 years) (n = 46)	-0.23 ± 4.46 <sup>*,†,‡</sup>	-4.52 ± 3.87 <sup>‡</sup>	-4.50 ± 3.83 <sup>‡</sup>	-5.43 ± 3.86	3.38 ± 2.88 <sup>*,†,‡</sup>	4.85 ± 3.44	4.78 ± 3.46	5.57 ± 3.65

VCM: vancomycin, TDM: therapeutic drug monitoring, CCr: creatinine clearance, VCM-TDM: SHIONOGI-VCM-TDM ver. 2009, ME: mean prediction error, MAE: mean absolute prediction error, SD: standard deviation, Conv: conventional, C-G: Cockcroft–Gault equation, Orita: Orita–Horio equation, \**P*-values ≤ 0.05 versus Conv Orita, †*P*-values ≤ 0.05 versus Fitted C-G, ‡*P*-values ≤ 0.05 versus Fitted Orita, *P*-values ≤ 0.05 were considered statistically significant by Bonferroni multiple comparison test.

**Table 3.** Predictive Performance of Initial VCM Trough Value of Each CCr Estimation Equation Using TDM Analysis Software MEEK

	ME ± SD				MAE ± SD			
	Conv C-G	Conv Orita	Fitted C-G	Fitted Orita	Conv C-G	Conv Orita	Fitted C-G	Fitted Orita
All patients (n = 308)	5.90 ± 5.51 <sup>*,†,‡</sup>	3.54 ± 5.74 <sup>†,‡</sup>	2.98 ± 5.86	2.78 ± 6.00	6.88 ± 4.21 <sup>*,†,‡</sup>	5.43 ± 3.99	5.30 ± 3.88	5.34 ± 3.90
Gender: Male (n = 198)	6.21 ± 5.57 <sup>*,†,‡</sup>	3.99 ± 5.82	3.88 ± 5.85	3.63 ± 6.05	7.18 ± 4.23 <sup>*,†,‡</sup>	5.77 ± 4.06	5.74 ± 4.02	5.81 ± 3.99
Gender: Female (n = 110)	5.34 ± 5.38 <sup>*,†,‡</sup>	2.71 ± 5.53 <sup>†,‡</sup>	1.35 ± 5.55	1.24 ± 5.61	6.34 ± 4.14 <sup>*,†,‡</sup>	4.82 ± 3.81	4.50 ± 3.50	4.47 ± 3.59
CCr ≥ 85 mL/min (n = 171)	5.18 ± 5.77	5.29 ± 5.74	5.18 ± 5.77	5.18 ± 5.77	6.59 ± 4.08	6.61 ± 4.15	6.59 ± 4.08	6.59 ± 4.08
CCr < 85 mL/min (n = 137)	6.79 ± 5.04 <sup>*,†,‡</sup>	1.35 ± 4.95 <sup>‡</sup>	0.23 ± 4.72	-0.22 ± 4.84	7.25 ± 4.35 <sup>†,‡</sup>	3.96 ± 3.24	3.69 ± 2.93	3.78 ± 3.02
Generation I (age: 20–39 years) (n = 35)	7.65 ± 5.41	7.69 ± 5.39	7.49 ± 5.55	7.49 ± 5.55	8.17 ± 4.57	8.20 ± 4.55	8.02 ± 4.74	8.02 ± 4.74
Generation II (age: 40–64 years) (n = 130)	5.86 ± 6.17 <sup>*,†,‡</sup>	4.56 ± 6.11 <sup>†,‡</sup>	3.58 ± 6.48	3.55 ± 6.44	7.31 ± 4.35 <sup>*,†,‡</sup>	6.29 ± 4.30	6.17 ± 4.08	6.05 ± 4.15
Generation III (age: 65–74 years) (n = 97)	5.32 ± 4.72 <sup>*,†,‡</sup>	1.86 ± 4.69	1.51 ± 4.52	1.17 ± 4.79	6.18 ± 3.52 <sup>*,†,‡</sup>	4.08 ± 2.95	3.89 ± 2.73	4.05 ± 2.79
Generation IV (age: 75 years) (n = 46)	5.88 ± 5.00 <sup>*,†,‡</sup>	1.00 ± 4.43	0.92 ± 4.60	0.40 ± 4.93	6.20 ± 4.59 <sup>*,†,‡</sup>	3.73 ± 2.53	3.75 ± 2.77	3.98 ± 2.88

VCM: vancomycin, TDM: therapeutic drug monitoring, CCr: creatinine clearance, MEEK: Vancomycin MEEK TDM analysis software ver 2.0, ME: mean prediction error, MAE: mean absolute prediction error, SD: standard deviation, Conv: conventional, C-G: Cockcroft–Gault equation, Orita: Orita–Horio equation, \**P*-values ≤ 0.05 versus Conv Orita, †*P*-values ≤ 0.05 versus Fitted C-G, ‡*P*-values ≤ 0.05 versus Fitted Orita, *P*-values ≤ 0.05 were considered as statistically significant by Bonferroni multiple comparison test.

the average value of the prediction error without considering whether they are under or over that of the actual value; thus, MAE is an indicator of the predictive accuracy.<sup>18)</sup> As shown in Table 2, the conventional C-G equation produced a higher ME (-1.56) than the other three equations (-5.10 to -3.65) in all patients using the VCM-TDM software. Thus, an ME value is closest to 0 point in the conventional C-G equation indicating that the prediction bias is the smallest. In contrast, using the MEEK software, the same trend was established. However, the values were positive; the conventional C-G equation (5.90)

produced a higher ME than the other equations (2.78–3.54) (Table 3). Thus, the prediction bias is the largest in the conventional C-G equation. These results are considered to be caused by the differences in estimated CCr values and PPK parameters between the two TDM analysis programs. The average CCr of each equation ranged from 102.0 to 132.7 mL/min (Table 1). The lowest CCr was obtained in the conventional C-G equation. In addition, fitted C-G and fitted Orita–Horio equations estimated a higher average CCr than the conventional equations.<sup>9)</sup> In contrast, previous research showed that lower

ME values (negative values) were obtained using VCM-TDM compared with MEEK (positive values); consequently, VCM-TDM has a risk of overdosing when determining settings and MEEK has a possibility of underestimation.<sup>16)</sup> Considering this, our results can be explained as follows: VCM-TDM tends to overdose,<sup>16)</sup> and therefore, the ME becomes close to 0 points if using the conventional C–G equation that has a lower calculated CCr value than the other equations. Thus, a high predictive accuracy (i.e., a low MAE) was obtained (Table 2). On the other hand, MEEK tends to underdose,<sup>16)</sup> and therefore, the ME moves away from 0 points when using the conventional C–G equation. Hence, a low predictive accuracy (i.e., a high MAE) was obtained. Similar trends were observed in generations II–IV and patients with CCr < 85 mL/min (Table 3).

In contrast, on using MEEK for generation I patients and patients with CCr ≥ 85 mL/min, there were no significant differences in MAE and ME between each of the CCr equations (Table 3). In patients with CCr ≥ 85 mL/min (calculated using conventional C–G equation), the CCr is fixed at 85 mL/min uniformly in the MEEK program. This function is set because the VCM clearance was not correlated in patients with CCr ≥ 85 mL/min in the parameters of the MEEK program.<sup>18)</sup> In generation I, only one patient had a CCr < 85 mL/min estimated using the conventional C–G and Orita–Horio equations, but all other patients had a CCr ≥ 85 mL/min (data not shown). Therefore, MAE and ME gave similar results between each equation. These results were similar to those obtained in previous research, which showed that MEEK has a risk of underdosing, especially in young patients.<sup>16)</sup>

In summary, the optimal combination of software and equations for the estimation of CCr for the initial dose setting of VCM were considered as follows. For VCM-TDM, when classified by age, the conventional C–G equation achieved the best predictive performance (i.e., the smallest MAE) except for generation I and II (Table 2). Therefore, the conventional C–G equation should be used except for these two generations. Although there is no significant difference, the conventional C–G equation may be better for generation I, whereas the conventional Orita–Horio equation may be better for generation II. In contrast, in the MEEK, the conventional C–G equation achieved the worst predictive performance (i.e., the highest MAE) except for generation I (Table 3). Thus, we recommend using the other three equations. For example, based on the smallest MAE, generation II: fitted Orita–Horio, generation III: fitted C–G, and generation IV: conventional Orita–Horio equations may be recommended (although there are no significant differences between three equations). In addition, as explained above, MEEK should not be employed for generation I because of the risk of underdosing.

In a previous study of the fitted C–G and fitted Orita–Horio equations, the predictive accuracy of the CCr was reported to be improved especially in the elderly; however, young individuals aged under 40 years could not be evaluated due to the lack of patients.<sup>9)</sup> However, differences in MAE and ME were not observed between each generation in this study (Table 2, 3). The reason for this is that the predictive performances of the equations are strongly influenced by PPK parameters built in the TDM analysis software as mentioned above.

Consequently, we suggest that accurate dose settings are not always achieved, even if accurate CCr equations based on the Japanese population are used. One of the reasons for this is that equations for renal function estimation (i.e., conven-

al C–G equation) used for PPK parameters are different from equations for drug dose settings. Thus, in order to utilize the new equations for renal function estimation for determining drug dose settings, it is necessary to conduct new PPK analysis, or at the very least, retrospectively verify the findings of previous studies.

Our study has several limitations. This study was conducted at a single center, and therefore, it is unclear if the same results can be obtained at other institutions. In addition, as this is a preliminary study using VCM dosing data, it is necessary to validate these results with other renal excretion-type drugs. Importantly, this study could not evaluate measured CCr, and therefore, it is unclear whether the calculated CCr values are truly accurate.

Notwithstanding, evidence in this study does indicate that an accurate renal function assessment does not always contribute to accurate drug dose settings, especially initial dose settings of VCM using TDM analysis software. We expect that these results will be useful to perform appropriate drug dose adjustments.

**Conflict of interests** The authors declare no conflict of interests.

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