学位論文

Exploration of optimal dosing regimens with linezolid for renal impairment patients

（腎機能障害者におけるリネゾリド至適投与法の探索）

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Abstract

Introduction: Linezolid is administered as a fixed dose to all patients despite evidence of overexposure and thrombocytopenia in renal impairment. The aims of this study were to evaluate the risk of thrombocytopenia and the utility of therapeutic drug monitoring (TDM), and to propose alternate dosing regimens in patients with non-dialysis-dependent (NDD) and hemodialysis-dependent (HDD) chronic kidney disease.

Methods: We retrospectively reviewed patients ≥ 13 years old for whom serum linezolid trough concentration (C_{min}) was measured during linezolid treatment. In NDD patients, patients with episodes of infection were divided into groups by presence of renal impairment (RI group) or absence of renal impairment (non-RI group), and by use of C_{min}-based TDM (TDM group) or not (non-TDM group) during linezolid treatment. In HDD patients, patients were divided into two groups depending on their initial dose of linezolid (standard dose of 600 mg every 12 h or initially reduced dose of 300 mg every 12 h/600 mg every 24 h).

Results: In the 108 NDD patients examined by multivariable analyses, renal impairment was independently associated with increased risk of thrombocytopenia (OR 2.90, 95%CI 1.13–7.44) and higher C_{min}. Analysis of the utility of TDM in the RI group showed that clinical failure rate was significantly lower in the TDM subgroup than in the non-TDM subgroup. Furthermore, in the RI group, dosage adjustments were needed in 90.5% of the TDM subgroup. All episodes administered a reduced dose of 300 mg every 12 h in the RI group showed $C_{min} \geq 2.0$ mg/L. Additional analysis of 53 episodes in which C_{min} was measured within 48 h after starting administration showed that the initial standard dose for 2 days was sufficient to rapidly reach an effective therapeutic concentration in the RI group. In HDD patients, 11 episodes of 8 chronic hemodialysis

patients were included; 5 were in the initially reduced-dose group. The cumulative incidence rates of thrombocytopenia and severe thrombocytopenia in the initially reduced-dose group were significantly lower than in the standard-dose group ($P < 0.05$). At the standard dose, the median C_{min} just before hemodialysis was 49.5 mg/L, and C_{min} at the reduced doses of 300 mg every 12 h and 600 mg every 24 h were 20.6 mg/L and 6.0 mg/L, respectively.

Conclusions: Empirical dose reduction to 300 mg every 12 h after administration of the initial fixed dose for 2 days and C_{min}-based TDM may improve safety outcomes while maintaining appropriate efficacy among NDD patients with renal impairment. In HDD patients, initial dose reduction to 600 mg per day should be implemented to reduce the risk of linezolid-induced thrombocytopenia.

Introduction

Linezolid is the first synthetic oxazolidinone agent that is used in the treatment of multi-drug resistant pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative staphylococci (MR-CoNS), vancomycin-resistant Enterococci, and *Mycobacterium tuberculosis* [1, 2].

Thrombocytopenia is exposure-dependent adverse effects of linezolid treatment and sometimes leads to discontinuation, even in the short periods [3]. Furthermore, this adverse event can increase the risk of mortality among critically ill patients [4, 5].

An exposure-response relationship has been clarified for thrombocytopenia and previous studies showed that linezolid trough concentration (C_{min}) values above 7–8 mg/L have consistently been associated with an increased risk of thrombocytopenia [6-11].

Linezolid dose adjustments for patients with non-dialysis-dependent chronic kidney disease (NDD-CKD) and end-stage renal disease (ESRD) are not currently required. Thus, it is easily prescribed for renal impairment and/or hemodialysis patients with Gram-positive infections [12]. However, the accumulating evidence indicates that the incidence of thrombocytopenia and subsequent linezolid discontinuation rates are significantly higher, and thrombocytopenia onset time is significantly shorter in patients with NDD-CKD and ESRD than those with normal renal function. This is caused by a systemic accumulation of linezolid in patients with NDD-CKD and ESRD [13-19].

Accordingly, therapeutic drug monitoring (TDM) and dose modification have been proposed by some authors to improve the safe and effective use of linezolid, especially in the population with renal impairment [6, 8, 11, 20].

Although linezolid overexposure has been reported to be related to several factors including renal impairment [11, 14, 20], drug-drug interactions [21], and illness severity [22], previous studies have suggested that a reduced dose of 300 mg every 12 h is better suited to non-dialysis dependent (NDD) patients with creatinine clearance (CL_{CR}) < 30 mL/min or estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, based on Monte Carlo simulations for sufficient efficacy and safety [11, 23]. However, real-world data from clinical practice to support this recommendation have remained lacking. Further, very few studies have assessed the accumulation of linezolid that occurs in hemodialysis-dependent (HDD) patients with repeated administration. Therefore, there is also a need for dosing regimen optimization to ensure the safety of hemodialysis patients receiving linezolid.

The aims of the present study were threefold: 1) to evaluate the relationships between renal impairment, thrombocytopenia and linezolid overexposure; 2) to evaluate whether TDM and TDM-guided dose modification could help prevent and/or recover from linezolid-induced myelosuppression, and prevent treatment failure with good outcome; and 3) to propose alternate initial and maintenance dosing regimens for NDD and HDD patients with impaired renal function using actual measurement data and simulation data of linezolid concentrations using recently developed simulation software [20, 24].

Methods

Study design

We conducted a monocentric, retrospective, cohort study from April 2013 to December 2019 among patients ≥ 13 years old who were treated with linezolid film-

coated tablets and/or injections (Zyvox®; Pfizer, Tokyo, Japan) because of suspected or documented Gram-positive bacterial infections at Toyama University Hospital. Patients with at least one linezolid serum C_{min} measured under steady-state conditions, at least 72 h after linezolid initiation or dose modification, during linezolid treatment were eligible for inclusion. Patients receiving continuous renal replacement therapy, and patients who were administered linezolid for tuberculosis or nontuberculous mycobacterial infections were excluded. Recurrent infection within the same patient was considered a distinct episode only if it occurred more than 1 week after the initial episode and once antimicrobial therapy had been completed. CL_{CR} was estimated using the Cockcroft-Gault formula ($CL_{CRC\text{-}G}$) and renal impairment was defined as a $CL_{CRC\text{-}G}$ $\leq$ 60 mL/min at baseline. Combination antimicrobial therapy was applied whenever clinically needed. In HDD patients, decisions regarding the modality and frequency of renal replacement therapy were made by the attending physician based on patient clinical characteristics. Most HDD patients received hemodialysis three times per week.

Linezolid TDM was performed via infectious disease (ID) consultation upon the request of attending physicians responsible for patients, and the results were reported back to them. After the ID consultation at the start of linezolid treatment, an initial dose reduction to 600 mg per day (300 mg every 12 h or 600 mg every 24 h) was recommended for all hemodialysis patients, but the decision was left to the discretion of the attending physician. C_{min} was measured using peripheral venous blood samples collected as clinical practice, just before the next administration after starting linezolid therapy. The times of the intravenous infusions or oral administrations and blood collections were carefully checked, and samples deemed inappropriate were excluded from the analysis. All serum samples obtained were stored at -80 °C until linezolid

trough measurement. C_{min} values were suitably measured, especially when ID physicians and/or attending physicians decided it necessary by reference to the course of platelet counts or C_{min} values, until the end of treatment. When linezolid $C_{min} > 10$ mg/L and thrombocytopenia occurred in the patient, linezolid dose adjustment was recommended by ID physicians, focused on controlling linezolid C_{min} within the optimal range of 2–8 mg/L [6, 8, 13]. TDM-based dose adjustments were performed finally at the discretion of the attending physician. Drug dosages were scaled linearly, with a minimum dose modification of 300 mg for the oral-route tablet.

Method of quantification

Steady-state serum C_{min} was defined as the total concentration just before the next administration or just before hemodialysis ≥ 72 h after linezolid initiation or dose modification. The elimination efficiency of linezolid by hemodialysis was calculated based on linezolid concentrations just before (C_{min}) and after hemodialysis (C_{HD}), as per the following equation:

$$\text{Elimination efficiency (\%)} = \frac{C_{min} - C_{HD}}{C_{min}} \times 100 \quad (1)$$

Serum concentrations of linezolid were analyzed by means of a validated HPLC analysis method, as previously described [20]. The intra- and inter-day coefficients of variation were always < 5% and the lower limit of detection was 0.1 mg/L. If multiple steady-state C_{min} values at the same dosage were measured in one episode, the mean value of all measurements from that episode was used for statistical analyses.

Analysis strategy

In NDD patients, episodes were divided into two subgroups, on the basis of the presence of renal impairment (renal impairment group; RI group) or absence of renal impairment (non-RI group). Patients were also divided into those for whom C_{min}-based TDM was used for dosage adjustment during linezolid treatment (TDM group) or in whom linezolid C_{min} values were measured and assessed only after the end of linezolid treatment, not during treatment (non-TDM group).

HDD patients were divided into two groups depending on their initial dose of linezolid administration. The first group received standard dosing (600 mg every 12 h), while the second group received reduced dosing (300 mg every 12 h or 600 mg every 24 h), which was initially administered under TDM.

Among most episodes where TDM was not performed, linezolid C_{min} values could not be measured during linezolid treatment due to delay of the requests for ID consultation from attending physician and/or difficulty in immediate measurements due to time constraints and limited human resources.

Data collection

Data were collected from the medical records of the study population. These include patient demographics, baseline laboratory and hematological parameters, type of infection, isolated microorganisms, linezolid dosage and serum C_{min} at each instance of TDM, number of all instances of TDM, number of instances of TDM under steady-state conditions, whether TDM for dosage adjustment was performed during linezolid treatment and whether it has resulted in any dose adjustments, treatment duration, as well as concomitant medications.

Clinical outcome

Episodes were defined as recovered if no clinical, biological and/or radiological evidence of infection was apparent at the end of treatment [6]. Failure was defined as any discontinuation of linezolid therapy before the end of treatment, either because of toxicity or because of persistence of infection [6]. Thirty-day reinfection was defined as infection caused by the same strain at the same infection site within 30 days after end of antimicrobial treatment.

Safety and tolerability outcome

In NDD patients, thrombocytopenia was defined as platelet count < 112.5 $\times 10^3/\mu L$ (75% lower limit of normal) at any time during treatment for episodes with platelet count at or above the lower limit of normal ($\geq$ 150 $\times 10^3/\mu L$) at baseline before administration, and 25% reduction from the baseline value for episodes with low platelet counts at baseline (75–149 $\times 10^3/\mu L$) [4, 11]. Severe thrombocytopenia was defined as platelet count < 75 $\times 10^3/\mu L$ for episodes with a normal baseline and platelet count < 50 $\times 10^3/\mu L$ for those with low baseline platelets, respectively [4, 11]. Recovery from thrombocytopenia was defined as the return and maintenance of platelet count to > 112.5 $\times 10^3/\mu L$ during therapy for episodes with platelet count at or above the lower limit of normal ($\geq$ 150 $\times 10^3/\mu L$) at baseline, or values > 75% of baseline values with low platelet count at baseline (75–149 $\times 10^3/\mu L$), after experiencing thrombocytopenia [4].

In HDD patients, to evaluate both thrombocytopenia and anemia as in the previous studies [8, 12, 19], thrombocytopenia and anemia were defined as unexplained reductions in platelet count and hemoglobin levels of >30% from patient baseline values

before linezolid administration. Severe thrombocytopenia was defined as a 50% reduction from the baseline, and the nadir was defined as the lowest value during the study period. The reduction rate was calculated using the following equation:

$$\text{Reduction rate (\%)} = \frac{\text{baseline} - \text{nadir}}{\text{baseline}} \times 100 \quad (2)$$

Recovery from thrombocytopenia in HDD patients was defined as the return and maintenance of platelet count values >70% of baseline values after experiencing thrombocytopenia.

Complete blood counts and serum chemistry profiles were monitored two or three times per week at the physician's discretion. The incidence, onset time, and platelet reduction rate of thrombocytopenia were also recorded.

Statistical analysis

The Kolmogorov-Smirnov test was used to assess the normality of data. Descriptive data are expressed as mean ± standard deviation or median with IQR, and continuous variables were compared using the Mann-Whitney test. Categorical variables were compared using the χ^2 test with Yates's correction or Fisher's exact test as necessary. In all analyses, we preliminarily confirmed the affect of multicollinearity of the covariates used in the statistical analysis. Univariate logistic regression analysis was used to investigate variables potentially associated with the occurrence of thrombocytopenia. Multivariate logistic regression analyses were performed with all the independent variables showing $P \leq 0.10$ on univariate analysis as well as with the main variable of renal impairment and variables deemed either clinically relevant or supported in the medical literature. Similarly, uni- and multivariate linear regression

analyses were used to identify independent predictors of higher C_{min} at the fixed dose. The time from linezolid initiation to developing thrombocytopenia was estimated using the Kaplan–Meier method and log-rank test. A value of $P \leq 0.05$ was considered statistically significant. All statistical analysis and plotting were performed using JMP Pro version 14.2.0 software (SAS Institute, Cary, NC).

Results

Toxicity and linezolid exposure in non-dialysis dependent patients

Figure 1 depicts the study flow chart. A total of 118 episodes in 108 NDD patients were included, comprising 35 episodes in 33 patients with renal impairment (RI group) and 83 episodes in 75 patients without renal impairment (non-RI group). All episodes except for six were initially administered as a fixed dose. The remaining 6 episodes were initially reduced to 600 mg per day because of lower body weight (≤ 45 kg) or elderly (≥ 88 years old) which were determined at the discretion of the attending physician. Demographics and clinical baseline characteristics stratified by CL_{CR} calculated using the Cockcroft-Gault formula ($CL_{CRC\text{-}G}$) are summarized in Table 1. Episodes mainly occurred in males (64.4%) with a median (range) age of 71 years (17-95 years) and a median weight of 57.1 kg (30.4–113.0 kg). The main indications for linezolid therapy were skin and soft tissue infections and surgical site infections followed by bacteremia, bone and joint infections, and respiratory tract infections. Skin and soft tissue infections and surgical site infections were more common in the non-RI group, and bacteremia was significantly more common in the RI group.

In the present analyses, a total of 118 episodes contributed 770 linezolid serum C_{min} concentrations. Median (IQR) number of instances of TDM were 6 (4–11) in the RI

group and 6 (2–8) in the non-RI group. Mean C_{min} at steady state for the fixed dose of 600 mg every 12 h in the RI group (25.6 ± 10.4 mg/L) was approximately double that in the non-RI group (14.1 ± 8.8 mg/L, $P < 0.0001$) (Table 1). Patients with episodes in the RI group were older and had lower height, body weight, body mass index, and baseline hemoglobin level. Median duration of linezolid therapy was 16 days in the RI group and 21 days in the non-RI group. Among concomitant medications, amlodipine was the most frequent co-prescribed agent both in total and in the RI group.

The rates of occurrence of thrombocytopenia in the two groups are also reported in Table 1. In total, 48 (40.7%) episodes developed thrombocytopenia and 22 (18.6%) developed severe thrombocytopenia. Thrombocytopenia occurred more frequently among episodes in the RI group (62.9%) than in the non-RI group (31.3%, $P = 0.0002$). Median time from initiation of therapy to development of thrombocytopenia was 12.5 days in both the RI and non-RI groups. In addition, renal impairment was independently associated with an increased risk of thrombocytopenia in uni- and multivariate conditional logistic regression analyses (OR 2.90, 95%CI 1.13–7.44) (Table 2 and 3). Platelet count at baseline was also found to be independently associated with thrombocytopenia.

Because many other confounding factors could affect linezolid overexposure, effects were further analyzed by multivariate linear regression using C_{min} collected after the fixed dose of 600 mg every 12 h (Table 4). Renal impairment and total body weight were independent predictors of higher C_{min} at the standard dose (R^2=0.30). However, linezolid C_{min} correlated linearly but weakly with $CL_{CRC\text{-}G}$ (adjusted R^2=0.234, $P < 0.0001$) (Supplemental Figure 1) and total body weight (0.142, $P < 0.0001$). Similarly, linezolid C_{min} correlated only weakly with other factors including age (adjusted

R^2=0.185, $P < 0.0001$) and body mass index (0.047, $P = 0.013$). Inter-episode coefficients of variation for linezolid C_{min} were 40.6% in the RI group and 61.7% in the non-RI group. Therefore, it should not be overlooked that renal function seems to partially explain the wide interindividual variability in C_{min} observed in this study population.

Usefulness of TDM in non-dialysis-dependent patients

In the analysis of the usefulness of TDM, the TDM group comprised 56 episodes from 52 patients and the non-TDM group comprised 62 episodes from 61 patients. Episodes in the two groups were further separated by the presence or absence of renal impairment. The distributions of C_{min} at the standard dose for both groups in the TDM and non-TDM groups were represented in Supplemental Figure 2. When assessing these episodes in terms of length of treatment and clinical outcome (Table 5), the duration of linezolid treatment was significantly longer in the TDM group than in the non-TDM group. No significant differences were seen among the TDM and non-TDM groups in failure rate due to persistence of infection. In addition, although thrombocytopenia occurred more frequently among episodes in the TDM group, failure rate due to toxicity and/or persistence of infection tended to be higher in the non-TDM group, but the difference did not reach statistical significance ($P = 0.052$). Failure rates did not differ significantly between the two groups in the non-RI group. On the other hand, although there was no significant difference with respect to the general characteristics, baseline hematological parameters and concomitant drug treatments, failure in general, and due to hematological toxicity were significantly lower in the TDM group of the RI group (Tables 5).

In the TDM group, dosage adjustments over time to avoid potential linezolid overexposure were needed in 90.5% of episodes in the RI group compared to only 62.9% of episodes in the non-RI group (P = 0.031) (Figure 2). TDM-guided dosage reductions allowed recovery from thrombocytopenia and prosecution of therapy until the planned end of treatment with good outcome in 12 (37.5%) of 32 episodes experiencing thrombocytopenia in the TDM group. Of the episodes needing dose reduction in the TDM group, all those episodes administered a reduced dose of 300 mg every 12 h in the RI group and in which steady-state C_{min} of the reduced dose could be measured (n=13) showed $C_{min} \geq 2.0$ mg/L, with no episode experiencing linezolid underexposure (Figure 3). On the other hand, in the non-RI group, 62.9% of episodes in patients were needed for dose reduction, but 23.1% (3/13) of these episodes were under exposure (< 2 mg/L) when administered reduced dose of 300 mg every 12 h (Figure 3). Mean C_{min} at the time of dose reduction to 300 mg every 12 h was significantly higher (10.1 ± 5.4 mg/L) than that in the non-RI group (n=13, 5.7 ± 3.4 mg/L, P = 0.038). Based on these results, a reduced dose of 300 mg every 12 h may be recommended as a maintenance dose in patients with renal impairment rather than patients with preserved renal function. However, despite using a reduced linezolid dose of 300 mg every 12 h, achieving linezolid C_{min} within the optimal range was seen in only 46.2% (6/13) of episodes in the RI group and 38.5% (5/13) in the non-RI group (Figure 3). TDM-based further reduction to 300 mg once daily was needed in 23.8% (5/21) of episodes in the RI group.

Initial and maintenance dosing strategy in non-dialysis-dependent patients

In an additional analysis of 53 episodes in which C_{min} was measured within 48 h of starting administration of a fixed 600 mg every 12 h, linezolid C_{min} of first measurement (first C_{min}) at 12, 24, 36, and 48 h after start administration were significantly higher in the RI group than in the non-RI group. The minimal first C_{min} in the RI group was the C_{min} of 2.9 mg/L at 24 h after start administration and all these episodes in the RI group were above the minimum value of optimal range (> 2 mg/L) even within 48 h after starting administration (Table 6 and Supplemental Figure 3). On the other hand, some first C_{min} of the episodes in the non-RI group were underexposure (Table 6 and Supplemental Figure 3).

In addition to the observational real-world data from clinical practice, we performed the linezolid dosing simulation of the hypothetical patient with mild renal impairment (male; 60 years old; total body weight, 70 kg; $CL_{CRC\text{-}G}$, 60 mL/min), using recently accepted simulation software "Pycsim" based on population pharmacokinetic and pharmacodynamic model [20, 24]. When linezolid was initially administered at a dose of 600 mg via hypothetical intravenous drip infusion for 60 minutes at 12-hour intervals for two days, and thereafter reduced dose of 300 mg via hypothetical intravenous drip infusion for 60 minutes every 12 h, the simulated C_{min} at the 48 h after start administration and steady-state C_{min} at the reduced dose of 300 mg every 12 h were 9.8 and 5.2 mg/L, respectively (Figure 4). These data suggested that initial administration of a fixed dose for 2 days may be sufficient to rapidly reach an effective therapeutic concentration and empirical dose reduction to 300 mg every 12 h under TDM control may provide the best balance of safety and efficacy, achieving therapeutic concentrations (2–8 mg/L) in NDD patients with $CL_{CRC\text{-}G} \leq 60$ mL/min.

Demographics and clinical characteristics of hemodialysis-dependent patients

A total of nine hemodialysis patients (12 episodes) were included in the study. However, during one of the episodes, the patient had developed septic shock and was subsequently excluded from the study because of reliance on continuous hemodiafiltration during linezolid treatment. Hence, 11 episodes of 8 chronic hemodialysis patients were finally included. Five episodes were in the initially reduced-dose group (300 mg every 12 h or 600 mg every 24 h). There were no episodes co-administered with rifampicin, omeprazole, amlodipine, amiodarone, or dexamethasone. All episodes except for one underwent TDM during the treatment. The median (IQR) duration of linezolid treatment was 17.5 days (13–30 days) in the standard-dose group and 17 days (8.5–19 days) in the initially reduced-dose group. There were no significant differences between the standard and the initially reduced-dose groups regarding patient demographics and clinical characteristics (Table 7).

Frequency of thrombocytopenia in hemodialysis-dependent patients and safety of the initially reduced dosing strategy

Thrombocytopenia developed in 81.8% of patients on linezolid therapy. In the standard-dose group, the median (IQR) time from initiation of linezolid to the occurrence of thrombocytopenia was 9 days (5–10.5 days) and 10 days (10–16 days) for the initially reduced-dose group. The standard-dose group showed a higher platelet count reduction rate relative to the initially reduced-dose group. There were no incidents of treatment failure (defined as toxicity or persistent infection) or reinfection after 30 days (Table 8).

Using Kaplan–Meier analysis, the cumulative incidence rates of thrombocytopenia and severe thrombocytopenia were significantly lower in the initially reduced-dose group than the standard-dose group ($P = 0.023$ and $P = 0.036$, log-rank test) (Figure 5).

All five episodes underwent TDM in the standard dose group required dose reduction to 600 mg per day (300 mg every 12 h or 600 mg every 24 h). They were implemented 3–6 days after the occurrence of thrombocytopenia, and the median (IQR) platelet count at the time of dose reduction was $110 \times 10^3/\mu L$ ($104–335 \times 10^3/\mu L$). Eight of nine episodes experienced thrombocytopenia in total were recovered from thrombocytopenia after the end of linezolid treatment. The remaining one episode in the standard dose group was recovered from thrombocytopenia at 11 days after TDM-based dose reduction during linezolid treatment.

Linezolid trough concentration at standard and reduced doses in hemodialysis-dependent patients

A total of 91 linezolid serum concentrations were measured. At the standard dose, the median (IQR) C_{min} just before hemodialysis (oral or intravenous route) was 49.5 mg/L (34.6–56.7 mg/L). The median (IQR) steady-state C_{min} at the reduced doses (300 mg every 12 h and 600 mg every 24 h) just before hemodialysis was 20.6 mg/L (19.5–26.3 mg/L) and 6.0 mg/L (3.9–16.0 mg/L), respectively (Figure 6).

The steady-state C_{min} at standard and reduced doses on the off-dialysis day could only be measured in one episode each (21.4 mg/L and 8.2 mg/L, respectively). The elimination efficiency of linezolid was found to be 26.4%, calculated using the 26 sets of consecutive concentrations measured just before and after intermittent hemodialysis.

There were three episodes where C_{min} was measured within 48 h of linezolid administration in the reduced-dose group. The values of C_{min} at 24 h were 8.3 mg/L and 7.6 mg/L, and the value at 48 h after linezolid administration was 5.5 mg/L.

Discussion

Several previous studies have shown that NDD patients with renal impairment more frequently experienced thrombocytopenia during fixed dose treatment [4, 11, 25]. Similarly, increasing evidence suggests that HDD patients treated with the conventional dose of linezolid are 6–9 times more likely to experience hematological toxicity than patients with normal renal function. In addition, the thrombocytopenia-associated linezolid discontinuation rate in hemodialysis patients was 62.5%, much higher than that among patients with normal renal function (2.3%) [19]. These high frequencies of thrombocytopenia in both NDD and HDD patients with impaired renal function may be due to increased linezolid concentrations and the absence of specific indications on dose adjustments according to renal function [15, 19, 25].

Indeed, the present study of NDD patients found that 3 times greater risk of thrombocytopenia with $CL_{CRC\text{-}G} \leq 60$ mL/min and the mean C_{min} of episodes with renal impairment was approximately double (25.6 ± 10.4 mg/L) that of episodes without renal impairment (14.1 ± 8.8 mg/L, $P < 0.0001$). Renal impairment was thus an independent predictor of higher C_{min} of the fixed dose, consistent with previous reports [6, 13].

Approximately 30–40% of the administered linezolid is excreted unchanged via the urine, and kidney function is thus a significant source of interpatient variability in linezolid clearance (CL) [26, 27]. However, many other covariates, including liver dysfunction, have been reported to affect the pharmacokinetics of linezolid [8, 28, 29];

therefore, a population pharmacokinetics approach would be preferred over the simplistic assessment of trough concentrations to evaluate the influence of renal impairment on linezolid clearance. Although we did not perform population pharmacokinetics analysis, in our previous analysis of linezolid population pharmacokinetics in 81 NDD patients of similar background, about 50% of elimination was found to be explained by renal clearance [20]. Similarly, several population pharmacokinetics studies using data obtained from clinical practice have also consistently demonstrated renal function to be one of the most important predictor of linezolid clearance [8, 23, 27, 30] and the results of the present study reconfirmed the necessity of effective linezolid dose adjustment for renal impairment patients.

To prevent and reduce the risk of developing thrombocytopenia, early intervention may be key. Previous studies have therefore suggested that a reduced dose of 300 mg every 12 h be recommended for NDD patients with CL_{CR} < 30 mL/min or eGFR < 60 mL/min/1.73 m^2, based on Monte Carlo simulations for sufficient efficacy and safety [11, 23]. However, to the best of our knowledge, no previous studies have supported this recommendation with actual measurement data from clinical practice. Furthermore, no studies appear to have considered the initial and maintenance dosing regimens separately.

Notably, in the present analyses, we found that an empirical dose reduction to 300 mg every 12 h under TDM control may provide the best balance of safety and efficacy in NDD patients with renal impairment, with no patients exposed to sub-therapeutic linezolid concentrations after dose reduction to 300 mg every 12 h (Figure 3). Further, we suggested that the initial fixed dose administration for 2 days was enough to rapidly reach an effective therapeutic concentration in the present additional analyses based on

the actual measurement data (Table 6 and Supplemental Figures 3) and the simulation data of linezolid concentrations using recently developed simulation software (Figures 4) [20, 24].

In patients with ESRD, hemodialysis is a significant means of linezolid elimination, as approximately 30% of the administered dose is removed during a 3 h hemodialysis session [31]. Brier et al. previously reported that the dose of linezolid does not need to be adjusted for hemodialysis patients. The recommendation was based on a study of single-dose administration during, but not after, hemodialysis among adults without infections [31]. This situation is clearly different from clinical settings, but due to the lack of evidence regarding the frequency of exposure-dependent adverse effects and linezolid concentrations on repeated standard dose administration, no specific indications for dose adjustments in hemodialysis patients have been provided.

To the best of our knowledge, this is the first cohort study to assess the linezolid accumulation occurring with repeated standard and reduced dosing, its elimination efficiency during hemodialysis in a clinical setting, and the safety of the initially reduced dosing regimen under TDM control in hemodialysis patients. The standard-dose group exhibited a higher reduction rate of platelet count than the initially reduced-dose group. The cumulative incidence rates of thrombocytopenia and severe thrombocytopenia in the initially reduced-dose group were significantly lower than in the standard-dose group. These are likely due to the early intervention via initial dose reduction to avoid linezolid overexposure, as patient demographics, baseline laboratory values, microorganisms, and the type of infection were not significantly different between the two groups. On the other hand, there were no significant differences in the rates of thrombocytopenia and severe thrombocytopenia between the standard and the

initially reduced-dose groups in the univariable analysis (Table 8). One of the reasons for this is that, despite using a reduced linezolid dose of 300 mg every 12 h/600 mg every 24 h, linezolid C_{min} within the optimal range was only seen in 30.8% (4/13), and exposure-dependent thrombocytopenia was eventually occurred even in the initially reduced dose group. Further reduction (for example, 300 mg per day) under TDM control may be needed in hemodialysis patients who require prolonged linezolid treatment.

Similarly, despite using a reduced linezolid dose of 300 mg every 12 h in the NDD patients, Crass et al. demonstrated the simulated probability of achieving linezolid C_{min} within the therapeutic range of 2–8 mg/L was only approximately 65% in simulated patients with eGFR < 60 mL/min/1.73 m^2. In the present study, achieving linezolid C_{min} within the therapeutic range was seen in only 46.2% of episodes in the RI group even after dose reduction to 300 mg every 12 h (Figure 3). Furthermore, TDM-based further reduction to 300 mg once daily was needed in 23.8% (5/21) of episodes in the RI group. On the other hand, in the non-RI group, 63% of episodes administered the fixed dose were also needed for dose reduction and despite using a reduced linezolid dose of 300 mg every 12 h, achieving linezolid C_{min} within the therapeutic range was seen in only 38.5% (5/13) in the non-RI group. All these observed results may be due to the large unexplained interindividual variation on clearance.

With regard to linezolid clearance in NDD patients, CL_{CR} was identified as the only covariate that significantly explained between subject variation [8], whereas variability due to other unknown factors still remained (the interindividual variability in clearance = 31.3%) in our previous study [27] and was nearly equivalent to previously

reported values (30.5% [8] and 35.2% [23]). Renal dose adjustments alone are thus unlikely to ensure adequate safety and efficacy of linezolid with prolonged therapy.

The use of TDM for patients who require prolonged linezolid treatment is thus essential to any intervention evaluating empirical dose reduction in patients with renal impairment. Also, even in patients with preserved renal function, although empirical dose reduction may not be recommended because of the presence of some episodes with underexposure, TDM and dose reduction under TDM control may also be needed to avoid overexposure and treatment failure. Pea et al. found that TDM-guided dose modification facilitates resolution of thrombocytopenia and safe continuation of therapy in one-third of patients who developed toxicity on standard empirical doses [6]. Similarly, we found that TDM-guided dosage adjustments to maintain the linezolid C_{min} range of 2–8 mg/L allowed recovery from thrombocytopenia and prosecution of therapy until the planned end of treatment, with good outcomes in 12 (37.5%) of 32 episodes experiencing thrombocytopenia among both patients with renal impairment and preserved renal function. We observed that TDM-based dose adjustments were also beneficial in hemodialysis patients, as they all required a reduced dose due to an extremely higher C_{min} at the standard dose and there were no episodes of treatment failure (due to toxicity or persistent infection) or reinfection. These observations were in line with a case–series study of peritoneal dialysis patients [18].

This study showed limitations inherent to the retrospective design and potential for confounding clinical conditions that cannot be excluded. We used multivariable models to control for confounding patient and clinical factors, but the potential for residual confounding remains. Furthermore, reliance on nominal times of administration and sample collection based on standards of care may have influenced the observed

interindividual variability and led to misspecification due to deviations from the sampling protocol in clinical practice. However, our results are consistent with previously published studies, which increases confidence in the results. In addition, due to the small sample size, it seems difficult to make a reliable conclusion about the availability of the optimal reduced dosing regimen in renal impairment and hemodialysis patients based solely on our findings.

Conclusions

In conclusion, our findings indicate that TDM-guided dose adjustment to maintain the linezolid C_{min} range of 2–8 mg/L may be beneficial in preventing treatment failure and in recovering from exposure-dependent thrombocytopenia. Based on the actual measurement data and the simulation data of linezolid concentrations using recently developed simulation software, initial fixed-dose administration for 2 days may be enough to rapidly reach an effective therapeutic concentration and empirical dose reduction to 300 mg every 12 h under TDM control may provide the best balance of safety and efficacy in NDD patients with $CL_{CRC\text{-}G} \leq 60$ mL/min. In HDD patients, initial dose reduction to 600 mg per day should be implemented to reduce the risk of linezolid-induced thrombocytopenia. Further clinical studies involving a large number of patients are necessary to validate our results.

List of Abbreviations

MRSA, methicillin-resistant *Staphylococcus aureus*

MR-CoNS, methicillin-resistant coagulase-negative staphylococci

C_{min}, trough concentration

NDD-CKD, non-dialysis-dependent chronic kidney disease

ESRD, end-stage renal disease

TDM, therapeutic drug monitoring

CL_{CR}, creatinine clearance

NDD, non-dialysis dependent

eGFR, estimated glomerular filtration rate

HDD, hemodialysis-dependent

CL_{CRC-G}, CL_{CR} calculated using the Cockcroft-Gault formula

ID, infectious disease

first C_{min}, C_{min} of first measurement

Declarations

Ethics approval and consent to participate

This study was performed in conformity with the Declaration of Helsinki after approval by the ethics review board of University of Toyama (approval number: clinical 24-118), and all patients provided informed consent regarding the publication of medical data.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this article.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1

Characteristics of episodes with or without renal impairment (RI group or non-RI group, respectively).

	All, 118 episodes in 108 patients	RI group, 35 episodes (29.7%) in 33 patients	Non-RI group, 83 episodes (70.3%) in 75 patients	P-value
Demographics				
Age (years), median (IQR)	71 (58.5–78)	78 (72–82)	67 (47–74)	<0.0001
Sex (male/female), (%/%)	76/42 (64.4/35.6)	22/13 (62.9/37.1)	54/29 (65.1/34.9)	0.84
Height (m), median (IQR)	1.61 (1.53–1.67)	1.56 (1.45–1.63)	1.64 (1.56–1.70)	0.0091
Body weight (kg), median (IQR)	57.1 (48.0–64.2)	49.4 (45.0–60.3)	59.3 (52.2–65.4)	0.0018
Body mass index (kg/m^2), median (IQR)	22.2 (20.1–23.7)	21.0 (18.9–22.9)	22.4 (20.6–24.6)	0.017
Laboratory, median (IQR)				
Serum creatinine (mg/dL)	0.65 (0.50–1.00)	1.20 (0.79–1.49)	0.57 (0.48–0.74)	<0.0001
$CL_{CRC\text{-}G}$	76.0 (49.2–105.4)	36.2 (26.9–49.4)	93.7 (72.0–118.7)	<0.0001
Total bilirubin (mg/dL)	0.4 (0.3–0.7)	0.4 (0.3–0.8)	0.4 (0.3–0.6)	0.85
Baseline hematological parameters				
Hemoglobin concentration (g/dL)	9.8 (8.5–11.6)	8.9 (8.3–10.2)	10.1 (8.7–11.9)	0.0081
Platelet count (×10^3/μL), median (IQR)	243 (177–319)	208 (151–284)	255 (181–247)	0.062
Low platelet count at baseline < 150 ×10^3/μL, n (%)	23 (19.5)	8 (22.9)	15 (18.1)	0.61
Episodes with platelet transfusion during therapy, n (%)	8 (6.8)	4 (11.4)	4 (4.8)	0.23
Episodes with DIC, n (%)	15 (12.7)	5 (14.3)	10 (12.1)	0.77
Main reason for linezolid				
Type of infection, n (%)				

Skin and soft tissue infections, and surgical site infections	47 (39.8)	9 (25.7)	38 (45.8)	0.063
Bacteremia	36 (30.5)	18 (51.4)	18 (21.7)	0.0021
Bone and joint infections	31 (26.3)	12 (34.3)	19 (22.9)	0.25
Respiratory tract infections	26 (22.0)	8 (22.86)	18 (21.69)	1.00
Intra-abdominal infections	8 (6.8)	4 (11.4)	4 (4.8)	0.23
Mediastinitis	7 (5.9)	2 (5.7)	5 (6.0)	1.00
Central nerve system infections	5 (4.2)	1 (2.9)	4 (4.8)	1.00
Endocarditis	4 (3.4)	2 (5.7)	2 (2.4)	0.58
Urinary tract infections	4 (3.4)	3 (8.6)	1 (1.2)	0.078
Unknown	6 (5.1)	1 (2.9)	5 (6.0)	0.67
Microbiological isolate, n (%)				
MRSA	63 (53.4)	18 (51.4)	45 (54.2)	0.84
MR-CoNS	25 (21.2)	8 (22.9)	17 (20.5)	0.81
Enterococci	7 (5.9)	3 (8.6)	4 (4.8)	0.42
Enterococcus faecalis	2 (1.7)	1 (2.9)	1 (1.2)	0.51
Enterococcus faecium	5 (4.2)	2 (5.7)	3 (3.6)	0.63
Corynebacterium species	6 (5.1)	4 (11.4)	2 (2.4)	0.063
Bacillus cereus	3 (2.5)	2 (5.7)	1 (1.2)	0.21
Other	8 (6.8)	4 (11.4)	4 (4.8)	0.23
No isolate, Unknown	11 (9.3)	2 (5.7)	9 (10.8)	0.50
Linezolid dosage and exposure				
Empirical/target therapy, n/n (%/%)	17/101 (14.4/85.6)	2/33 (5.7/94.3)	15/68 (18.1/81.9)	0.093
Dose (mg/kg/day), median (IQR)	20.7 (17.8–24.2)	23.6 (18.5–26.7)	20.0 (17.3–22.3)	0.017
Mean C_{min} of fixed doses at steady state (mg/L), mean ± SD	17.3 ± 10.5	25.6 ± 10.4	14.1 ± 8.8	<0.0001
Number of all TDM instances, median (IQR)	6 (3–8)	6 (4–11)	6 (2–8)	0.33
Number of TDM instances under steady-state conditions, median (IQR)	3 (2–6)	3 (2–6)	3 (2–6)	0.47
Episodes with TDM assessment performed during linezolid treatment, until end of treatment	56 (47.5)	21 (60.0)	35 (42.2)	0.11

Episodes needing dosage adjustments to avoid overexposure, n (%)	42/56 (73.2)	19/21 (90.5)	22/35 (62.9)	0.031
Duration of linezolid treatment (days), median (IQR)	20 (11–37.5)	16 (11–40)	21 (11–36)	0.96
Co-treatment, n (%)				
Amlodipine	16 (13.6)	7 (20.0)	9 (10.8)	0.24
Omeprazole	15 (12.7)	4 (11.4)	11 (13.3)	1.00
Rifampicin	11 (9.3)	5 (14.3)	6 (7.2)	0.30
Amiodarone	2 (1.7)	1 (2.9)	1 (1.2)	0.51
Dexamethasone	2 (1.7)	1 (2.9)	1 (1.2)	0.51
Other antimicrobials, n (%)				
Meropenem	26 (22.0)	7 (20.0)	19 (22.9)	0.81
Doripenem	10 (8.5)	1 (2.9)	9 (10.8)	0.28
Piperacillin/tazobactam	15 (12.7)	7 (20.0)	8 (9.6)	0.14
Daptomycin	2 (1.7)	1 (2.9)	1 (1.2)	0.51
Ciprofloxacin	5 (4.2)	0 (0.0)	5 (6.0)	0.32
Levofloxacin	7 (5.9)	0 (0.0)	7 (8.4)	0.10
Micafungin	7 (5.9)	2 (5.7)	5 (6.0)	1.00
Liposomal amphotericin B	4 (3.4)	2 (5.7)	2 (2.4)	0.58
Voriconazole	3 (2.5)	0 (0.0)	3 (3.6)	0.55
Type of toxicity, n (%)				
Thrombocytopenia	48 (40.7)	22 (62.9)	26 (31.3)	0.0002
Median time from initiation of therapy to development of thrombocytopenia (n=48), median days (IQR)	12.5 (9.0–15.8)	12.5 (10.8–15)	12.5 (2.8–17.3)	0.56
Severe thrombocytopenia	22 (18.6)	10 (28.6)	12 (14.5)	0.12

Abbreviations: RI, renal impairment; CL_{CRC-G}, creatinine clearance calculated using the Cockcroft-Gault formula DIC, disseminated intravascular coagulopathy; MRSA, methicillin-resistant *Staphylococcus aureus*; MR-CoNS, methicillin-resistant coagulase-negative staphylococci; TDM, therapeutic drug monitoring

Table 2

Univariate evaluation of risk factors for development of thrombocytopenia.

	Episodes with thrombocytopenia, n=48 (40.7%)	Episodes without thrombocytopenia, n=70 (59.3%)	P-value
Demographics			
Age (years), median (IQR)	72 (66–77.8)	69 (49.5–78)	0.28
Sex (male/female), (%/%)	32/16 (66.7/33.3)	44/26 (62.9/37.1)	0.70
Height (m), median (IQR)	1.60 (1.51–1.67)	1.63 (1.54–1.68)	0.18
Body weight (kg), median (IQR)	51.5 (45.4–60.2)	60.0 (53.3–65.1)	0.0048
Body mass index (kg/m^2), median (IQR)	21.1 (19.1–23.3)	22.5 (20.7–25.3)	0.0082
Laboratory, median (IQR)			
Serum creatinine (mg/dL)	0.80 (0.52–1.26)	0.60 (0.50–0.83)	0.040
$CL_{CRC\text{-}G} \leq 60$ mL/min	22 (45.8)	13 (18.6)	0.0020
Total bilirubin (mg/dL)	0.4 (0.3–0.6)	0.5 (0.3–0.73)	0.43
Baseline haematological parameters, median (IQR)			
Hemoglobin concentration (g/dL), median (IQR)	9.3 (8.4–10.5)	10.0 (8.7–11.8)	0.033
Platelet count ($\times 10^3/\mu L$), median (IQR)	205 (143.5–254.5)	303.5 (195–382.5)	<0.0001
Low platelet count at baseline < 150 $\times 10^3/\mu L$, n (%)	13 (27.1)	10 (14.3)	0.101
Episodes with platelet transfusion during therapy, n (%)	6 (12.5)	2 (2.9)	0.061
Episodes with DIC, n (%)	9 (18.8)	6 (8.6)	0.16
Main reason for linezolid			
Type of infection, n (%)			
Skin and soft tissue infections, and surgical site infections	17 (35.4)	30 (42.9)	0.45
Bacteraemia	19 (39.6)	17 (24.3)	0.103
Bone and joint infections	13 (27.1)	18 (25.7)	1.00
Respiratory tract infections	9 (18.8)	17 (24.3)	0.51
Intra-abdominal infections	3 (6.3)	5 (7.1)	1.00
Mediastinitis	4 (8.3)	3 (4.3)	0.44
Central nervous system infections	0 (0.0)	5 (7.1)	0.079
Endocarditis	2 (4.2)	2 (2.9)	1.00

Urinary tract infections	2 (4.2)	2 (2.9)	1.00
Unknown	3 (6.3)	3 (4.3)	0.69
Linezolid dosage and exposure			
Empirical/target therapy, n/n (%/%)	6/48 (12.5/87.5)	11/59 (15.7/84.3)	0.79
Mean C_{min} of fixed doses in steady state (mg/L), mean ± SD	20.6 ± 10.8	15.3 ± 9.8	0.0023
Duration of linezolid treatment (days), median (IQR)	21 (12–42.8)	19.5 (10.8–34.3)	0.29

Abbreviations: $CL_{CRC\text{-}G}$, creatinine clearance calculated using the Cockcroft-Gault formula; DIC, disseminated intravascular coagulopathy

Table 3

Multivariate conditional logistic regression analysis of variables associated with occurrence of thrombocytopenia.

	OR (95%CI)	P-value
Male	1.25 (0.52–3.01)	0.62
Body mass index (kg/m^2) (per 1-kg/m^2 increment)	0.93 (0.72–1.08)	0.25
$CL_{CRC-G} \leq 60$ mL/min	2.90 (1.13–7.44)	0.027
Hemoglobin concentration (g/dL) (per 1-g/dL increment)	0.89 (0.72–1.08)	0.23
Platelet count ($\times 10^3/\mu L$) (per 1.0 $\times 10^3/\mu L$ increment)	0.993 (0.989–0.997)	0.0002
Bacteraemia	1.44 (0.51–4.01)	0.49
Duration of linezolid treatment (days) (per 1-day increment)	1.010 (0.989–1.031)	0.36

R^2=0.189

Abbreviations: CL_{CRC-G}, creatinine clearance calculated using the Cockcroft-Gault formula

Table 4

Uni- and multivariate linear regression analysis of variables associated with linezolid C_{min} at standard dose of 600 mg every 12 h.

Variables	Univariate analysis		Multivariate analysis[a]	
	Unstandardized β coefficient (95%CI)	P-value	Unstandardized β coefficient (95%CI)	P-value
Male	-2.81 (-6.95 to 1.34)	0.18		
Age (years) (per 1-year increment)	0.285 (0.173 to 0.396)	<0.0001		
Height (m) (per 1-m increment)	-33.71 (-51.35 to -16.07)	0.0003		
Body weight (kg) (per 1-kg increment)	-0.294 (-0.427 to -0.160)	<0.0001	-0.208 (-0.335 to 0.081)	0.0016
$CL_{CRC-G} \leq 60$ mL/min	11.37 (7.397 to 15.345)	<0.0001	4.777 (2.793 to 6.760)	<0.0001
Total bilirubin > 1.2 mg/dL	1.111(-2.960-5.199)	0.59		
Co-treatment				
Omeprazole	-1.097 (-7.273 to 5.079)	0.73		
Amiodarone	4.676 (-1.243 to 10.595)	0.12		
Amlodipine	1.037 (-13.885 to 15.960)	0.89		
Rifampicin	2.236 (-5.028 to 9.501)	0.54		
Dexamethasone	0.426 (-14.450 to 15.350)	0.96		

[a] R^2=0.301

Abbreviation: CL_{CRC-G}, creatinine clearance calculated using the Cockcroft-Gault formula

Table 5

Clinical outcome and length of treatment in TDM and non-TDM groups, further separated by presence or absence of renal impairment (RI or non-RI groups).

Total	TDM group, n=56 (47.5%)	Non-TDM group, n=62 (52.5%)	P-value
Recovery, n (%)	38 (67.9)	35 (56.5)	0.26
Duration of linezolid treatment (days), median (IQR)	30 (19.5–45)	12 (9–21.3)	<0.0001
Failure, n (%)	14 (25.0)	27 (43.6)	0.052
Failure due to persistence of infection, n (%)	6 (10.7)	2 (3.2)	0.15
Failure due to hematological toxicity, n (%)	10 (17.9)	18 (29.0)	0.20
Failure due to other toxicity, n (%)	3 (5.4)	8 (12.9)	0.21
Thirty-day reinfection, n (%)	5 (8.9)	4 (6.5)	0.73
Thrombocytopenia	32 (66.7)	16 (33.3)	0.0007
RI group	TDM group, n=21, (60.0%)	Non-TDM group, n=14, (40.0%)	P-value
Recovery, n (%)	15 (71.4)	5 (35.7)	0.080
Duration of linezolid treatment (days), median (IQR)	34 (20–46)	11.5 (8.8–13.3)	<0.0001
Failure, n (%)	3 (14.3)	9 (64.3)	0.0038
Failure due to persistence of infection, n (%)	1 (4.8)	0 (0.0)	1.00
Failure due to hematological toxicity, n (%)	2 (9.5)	8 (57.1)	0.0056
Failure due to other toxicity, n (%)	0 (0.0)	2 (14.3)	0.15
Thirty-day reinfection, n (%)	3 (14.3)	1 (7.1)	0.64
Thrombocytopenia	17 (81.0)	5 (35.7)	0.012
Non-RI group	TDM group, n=35 (42.2%)	Non-TDM group, n=48 (57.8%)	P-value
Recovery, n (%)	23 (65.7)	30 (62.5)	0.82
Duration of linezolid treatment (days), median (IQR)	29 (19–45)	13.5 (9–22.8)	<0.0001
Failure, n (%)	18 (37.5)	11 (31.4)	0.64

Failure due to persistence of infection, n (%)	2 (4.2)	5 (14.3)	0.13
Failure due to hematological toxicity, n (%)	10 (20.8)	8 (22.9)	1.00
Failure due to other toxicity, n (%)	6 (12.5)	3 (8.6)	0.73
Thirty-day reinfection, n (%)	3 (6.3)	2 (5.7)	1.00
Thrombocytopenia	15 (42.9)	11 (22.9)	0.060

Abbreviations: TDM, therapeutic drug monitoring; RI, renal impairment

Table 6

Linezolid C_{min} of the first measurement (first C_{min}) at 12, 24, 36, or 48 h after starting administration of fixed 600 mg every 12 h and ratio of first C_{min} to mean C_{min} under steady state in the RI group and non-RI group.

Time after starting administration of fixed 600 mg every 12 h (h)	Linezolid C_{min} of first measurement (first C_{min}), mean ± SD (range)					Ratio of first C_{min} to mean C_{min} under steady state, median (IQR)				
	RI group	n	Non-RI group	n	P-value	RI group	n	Non-RI group	n	P-value
12	8.9 ± 0.4 (8.6–9.4)	3	6.2 ± 3.7 (0.2–14.0)	17	0.090	52.0 (24.3–75.6)	3	52.0 (26.4–80.7)	17	0.96
24	12.3 ± 8.8 (2.9–24.3)	7	8.3 ± 3.6 (4.8–14.2)	5	0.75	81.8 (64.4–118.3)	7	58.2 (27.3–64.4)	5	0.051
36	18.8 ± 3.6 (16.2–21.3)	2	9.6 ± 7.8 (0.5–23.3)	7	0.19	67.6 (41.7–102.0)	2	61.3 (45.1–77.5)	7	0.88
48	25.3 ± 9.6 (15.8–36.1)	4	8.7 ± 4.8 (1.4–14.7)	8	0.0085	62.3 (45.8–79.1)	4	79.1 (55.0–86.8)	8	0.44
Total	15.7 ± 9.5 (2.9–36.1)	16	7.7 ± 4.9 (0.2–23.3)	37	0.0019	58.9 (37.8–89.1)	16	60.5 (38.7–79.9)	37	0.71

Abbreviations: C_{min}, trough concentration, first C_{min}, C_{min} of first measurement; RI, renal impairment

Table 7

Characteristics of episodes in the standard-dose group and initially reduced-dose group.

Characteristics	All, n=11	Standard dose group, n=6 (54.5%)	Initially reduced dose group, n=5 (45.5%)	P-value
Demographics				
Age (years), median (IQR)	56 (41–60)	55 (42–64)	59 (41–76)	0.78
Sex (male/female), (%/%)	8/3 (72.7/27.3)	4/2 (66.7/33.3)	4/1 (80.0/20.0)	1.00
Body weight (kg), median (IQR)	56.7 (46.3–64.0)	53.2 (42.3–78.3)	56.7 (42.8–60.4)	0.93
Body mass index (kg/m^2), median (IQR)	19.8 (17.1–22.6)	21.2 (16.1–26.1)	19.8 (17.7–21.1)	0.65
Laboratory, median (IQR)				
Serum creatinine (mg/dL)	6.8(5.9–9.8)	6.8 (5.6–8.5)	8.5 (6.1–10.6)	0.31
eGFR	6.1 (4.5–8.5)	6.8 (5.7–8.3)	4.5 (4.2–9.3)	0.65
Total bilirubin (mg/dL)	0.2 (0.2–0.4)	0.3 (0.2–0.4)	0.2 (0.2–0.4)	1.00
Baseline hematological parameters				
Hemoglobin concentration (g/dL), median (IQR)	9.3 (8.3–10.2)	9.7 (8.2–10.3)	8.8 (7.3–10.4)	0.78
Platelet count (×10^3/μL), median (IQR)	200 (169–249)	240 (184–488)	180 (166–201)	0.12
Main reason for linezolid				
Type of infection, n (%)				
Skin and soft tissue infections, and surgical site infections	8 (72.7)	3 (50.0)	5 (100.0)	0.18
Mediastinitis	3 (27.3)	2 (33.3)	1 (20.0)	1.00
Bone and joint infections	2 (18.2)	1 (16.7)	1 (20.0)	1.00
Respiratory tract infections	1 (9.1)	1 (16.7)	0 (0.0)	1.00
Microbiological isolate, n (%)				
MRSA	5 (45.5)	3 (50.0)	2 (40.0)	1.00
MR-CoNS	3 (27.3)	2 (33.3)	1 (20.0)	0.81
No isolate, Unknown	3 (27.3)	1 (16.7)	2 (40.0)	0.55
Linezolid dosage and exposure				
Empirical/target therapy, n/n (%/%)	3/8 (27.3/72.7)	0/6 (0.0/100.0)	2/5 (40.0/60.0)	0.061
Dose (mg/kg/day), median (IQR)	-	22.7 (15.5–28.6)	10.6 (10.0–15.3)	0.022

Number of all TDM instances, median (IQR)	10 (3–12)	10.5 (2.8–14.5)	5 (2.5–11.5)	0.52
Episodes with TDM assessment performed during linezolid treatment, until end of treatment	10 (90.9)	5 (83.3)	5 (100.0)	1.00
Duration of linezolid treatment (days), median (IQR)	17 (13–21)	17.5 (13–30)	17 (8.5–19)	0.31
Co-treatment, n (%)				
Levothyroxine	6 (54.5)	2 (33.3)	4 (80.0)	0.24
Other antimicrobials, n (%)				
Meropenem	2 (18.2)	1 (16.7)	1 (20.0)	1.00
Piperacillin/tazobactam	2 (18.2)	2 (33.3)	0 (0.0)	0.45

Abbreviations: eGFR, estimated glomerular filtration rate; MR-CoNS, methicillin-resistant coagulase-negative staphylococci; TDM, therapeutic drug monitoring

Table 8

Linezolid-related adverse events and clinical outcome in the standard-dose group and initially reduced-dose group.

Variables	All, n=11	Standard-dose group, n=6 (54.5%)	Initially reduced-dose group, n=5 (45.5%)	P-value
Type of toxicity, n (%)				
Thrombocytopenia	9 (81.8)	6 (100.0)	3 (60.0)	0.18
Median time from initiation of therapy to development of thrombocytopenia (n=9), median days (IQR)	10 (6.5–11)	9 (5–10.5)	10 (10–16)	0.18
Severe thrombocytopenia	6 (54.5)	5 (83.3)	1 (20.0)	0.080
Nadir platelet count ($\times 10^3/\mu L$), median (range)	97 (54–208)	81.5 (57–208)	131 (54–180)	0.65
Reduction rate of platelet count (%), median (IQR)	57.8 (35.5–67.0)	63.1 (52.7–76.1)	35.5 (6.4–54.7)	0.055
Anemia	7 (63.6)	5 (83.3)	2 (40.0)	0.24
Gastrointestinal intolerance	2 (18.2)	2 (33.3)	0 (0.0)	0.45
Hyponatremia	2 (18.2)	2 (33.3)	0 (0.0)	0.45
Clinical outcome, n (%)				
Failure	0 (0.0)	0 (0.0)	0 (0.0)	-
Thirty-day reinfection	0 (0.0)	0 (0.0)	0 (0.0)	-

Figure legends

Figure 1

Study flow.

Abbreviations: C_{min}, trough concentration; CRRT, continuous renal replacement therapy; HD, hemodialysis; TDM, therapeutic drug monitoring; RI, renal impairment

Figure 2

Boxplots of C_{min} at the standard dose in the RI and non-RI groups among the episodes in the TDM group.

For each boxplot, the horizontal line across the box within each box represents the median, each box represents the range between the 25th and 75th percentiles, the two whiskers represent the minimum and maximum values that are within 1.5 × IQR, and points beyond the whiskers represent outliers. Closed circles represent C_{min} values of the episodes in which dose adjustment was performed, and open circles represent C_{min} values of the episodes in which dose adjustment was not performed.

Abbreviations: C_{min}, trough concentration; RI, renal impairment, TDM, therapeutic drug monitoring

Figure 3

Boxplots of C_{min} after dose reduction to 300 mg every 12 h in the RI and non-RI groups.

For each boxplot, the horizontal line across the box within each box represents the median, each box represents the range between the 25th and 75th percentiles, the two whiskers represent the minimum and maximum values that are within 1.5 × IQR, and points beyond the whiskers represent outliers. Open circles represent C_{min} < 2.0 mg/L, closed circles represent C_{min} within the desired range of 2–8 mg/L, and open square represent C_{min} values of overexposure (> 8 mg/L).

Abbreviations: C_{min}, trough concentration; RI, renal impairment

Figure 4

Simulation of linezolid concentrations using Pycsim software.

Shown are screenshots of the application running in the browser-window. This capture is the result of simulation performed after input of the dosing records based on hypothetical patients with mild renal impairment. The dosing records were inputted as initial administration at a dose of 600 mg via hypothetical intravenous drip infusion for 60 minutes at 12-hour intervals for two days, and thereafter reduced dose administration of 300 mg via hypothetical intravenous drip infusion for 60 minutes every 12 h. The final output is a file consisting of both parts; the left column represents population prediction with pharmacokinetic parameters, the right column represents the simulation curve of total and unbound concentration (black lines: population prediction).

Figure 5

Kaplan-Meier curves of thrombocytopenia (**A**) and severe thrombocytopenia (**B**) development time after the initiation of linezolid therapy in the standard-dose group (red) and initially reduced-dose group (blue).

Figure 6

Boxplots of trough concentration (C_{min}) at the standard dose and after a dose reduction to 600 mg every 24 hours on hemodialysis days. For each boxplot, the horizontal line across the box represents the median, each box represents the range between the 25th and 75th percentiles, the two whiskers represent the minimum and maximum values that are within 1.5 × IQR, and points beyond the whiskers represent outliers. Closed circles represent C_{min} administered at the intravenous route and open circles represent C_{min} administered at the oral route.

Supplemental Figure 1

Relationship between linezolid C_{min} of the fixed dose of 600 mg every 12 h and creatinine clearance as estimated using the Cockcroft-Gault formula (CL_{CRC-G}).

Abbreviations: C_{min}, trough concentration; CL_{CRC-G}, creatinine clearance calculated using the Cockcroft-Gault formula

Supplemental Figure 2

Boxplots of C_{min} at the standard dose in the TDM group and non-TDM group.

For each boxplot, the horizontal line across the box within each box represents the median, each box represents the range between the 25th and 75th percentiles, the two whiskers represent the minimum and maximum values that are within 1.5 × IQR, and points beyond the whiskers represent outliers. Closed circles represent C_{min} at the standard dose.

Abbreviations: C_{min}, trough concentration; TDM, therapeutic drug monitoring

Supplemental Figure 3

Dot plots represent the distribution of linezolid C_{min} of the first measurement (first C_{min}) at 12, 24, 36, or 48 h after starting administration of fixed 600 mg every 12 h in the RI group (A) and the non-RI group (B).

Open circles represent C_{min} < 2.0 mg/L, closed circles represent C_{min} within the desired range of 2–8 mg/L, and open square represent C_{min} values of overexposure (> 8 mg/L).

Abbreviations: C_{min}, trough concentration; fist $C_{min,}$ C_{min} of first measurement; RI, renal impairment

Figure 1

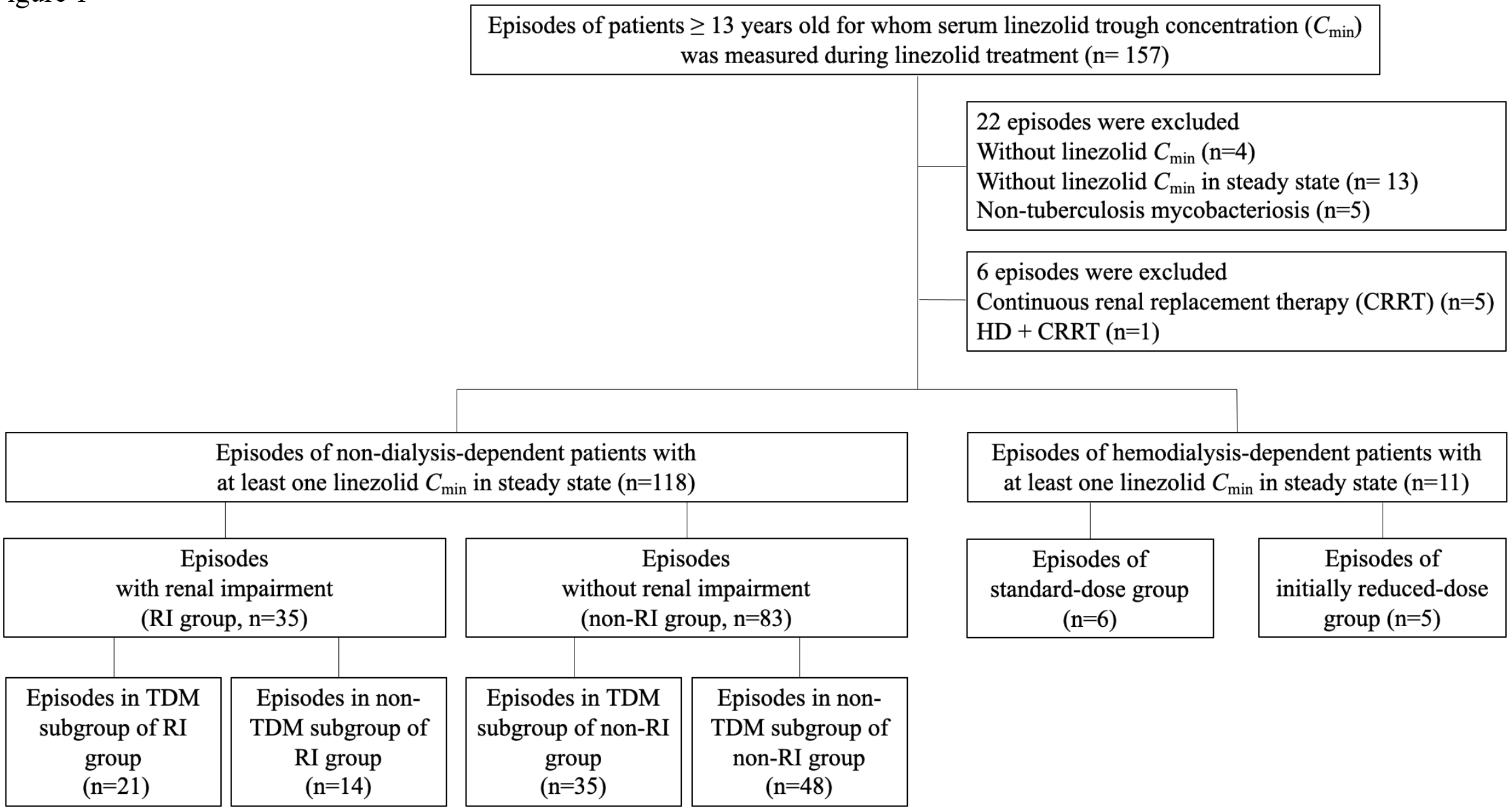

Episodes of patients ≥ 13 years old for whom serum linezolid trough concentration (C_{min}) was measured during linezolid treatment (n= 157)
22 episodes were excluded
Without linezolid C_{min} (n=4)
Without linezolid C_{min} in steady state (n= 13)
Non-tuberculosis mycobacteriosis (n=5)
6 episodes were excluded
Continuous renal replacement therapy (CRRT) (n=5)
HD + CRRT (n=1)
Episodes of non-dialysis-dependent patients with at least one linezolid C_{min} in steady state (n=118)
Episodes of hemodialysis-dependent patients with at least one linezolid C_{min} in steady state (n=11)
Episodes with renal impairment (RI group, n=35)
Episodes without renal impairment (non-RI group, n=83)
Episodes of standard-dose group (n=6)
Episodes of initially reduced-dose group (n=5)
Episodes in TDM subgroup of RI group (n=21)
Episodes in non-TDM subgroup of RI group (n=14)
Episodes in TDM subgroup of non-RI group (n=35)
Episodes in non-TDM subgroup of non-RI group (n=48)

Figure 2

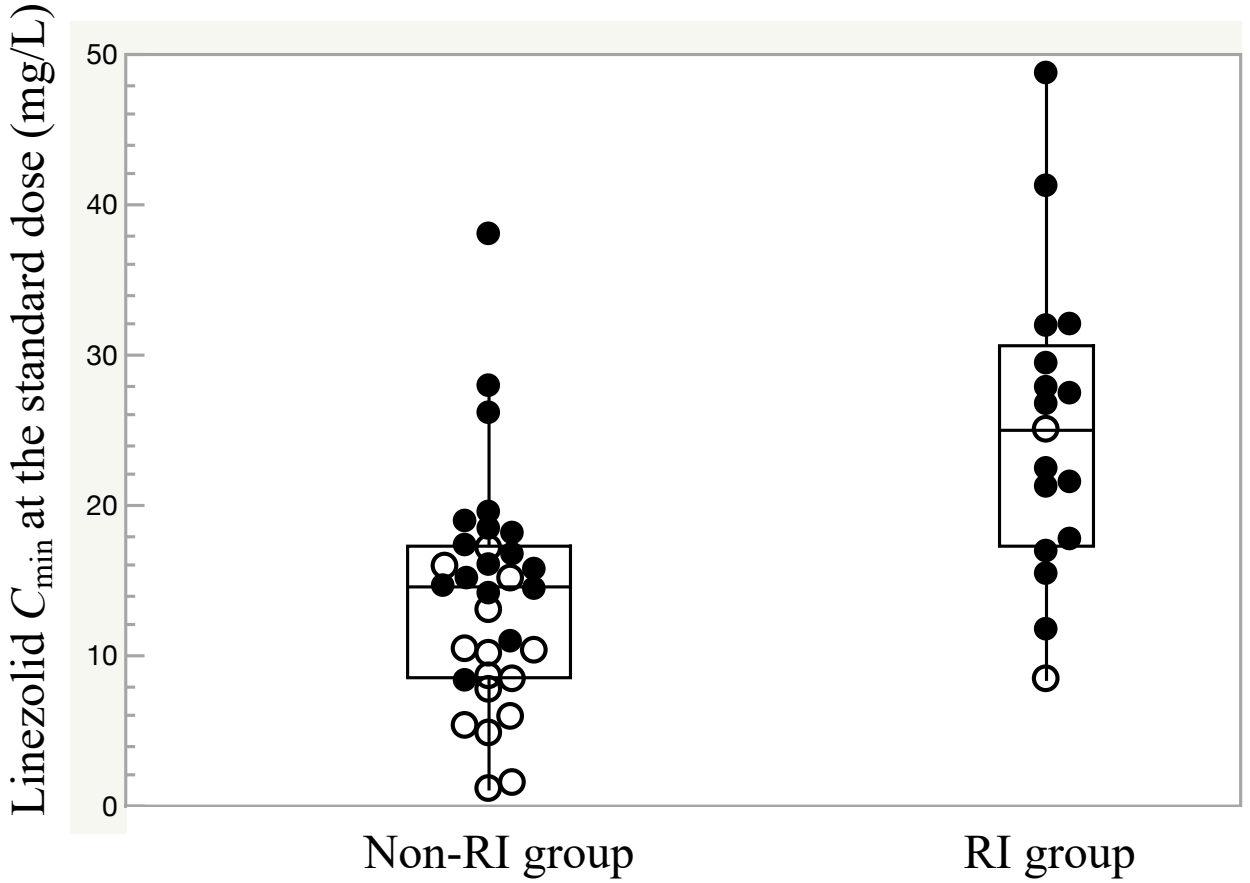

Linezolid C_{min} at the standard dose (mg/L)
50
40
30
20
10
0
Non-RI group
RI group

Figure 3

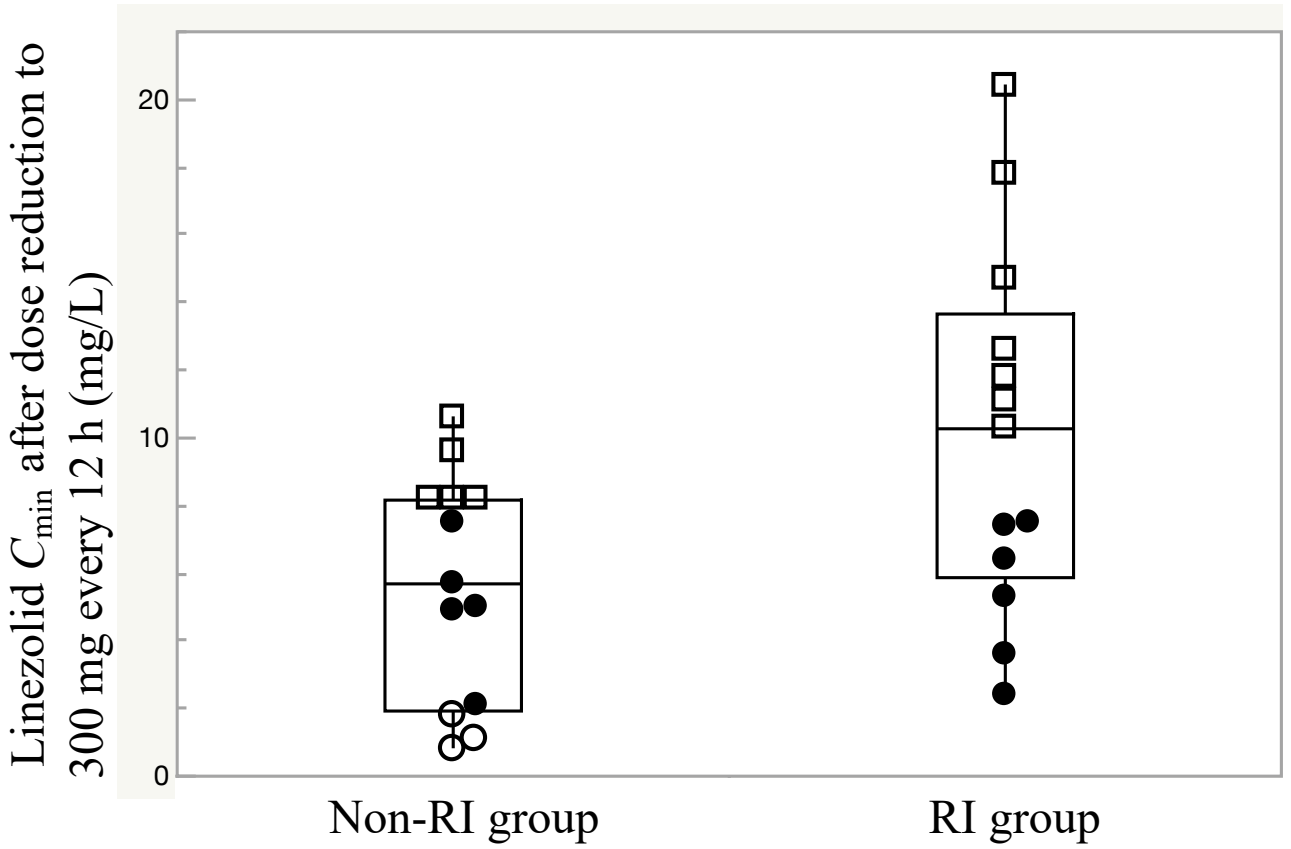

Linezolid C_{min} after dose reduction to 300 mg every 12 h (mg/L)
20
10
0
Non-RI group
RI group

Figure 4

Home | Simulation | References

Summary | Used data | Simulation result

Observation / Prediction

Total concentration (mg/L)

Date	Erapced time (day)	Observation	Population prediction	Individual prediction
-	-	-	-	-

Unbound concentration (mg/L)

Date	Erapced time (day)	Observation	Population prediction	Individual prediction
-	-	-	-	-

Platelet count (/μL)

Date	Erapced time (day)	Observation	Population prediction	Individual prediction
-	-	-	-	-

PK parameter

Parameter	Population mean
Clearance (L/h)	3.10
Volume of central (L)	22.90
Volume of peripheral (L)	24.70
Inter-compartment clearance (L/h)	10.90

Black line: population prediction;

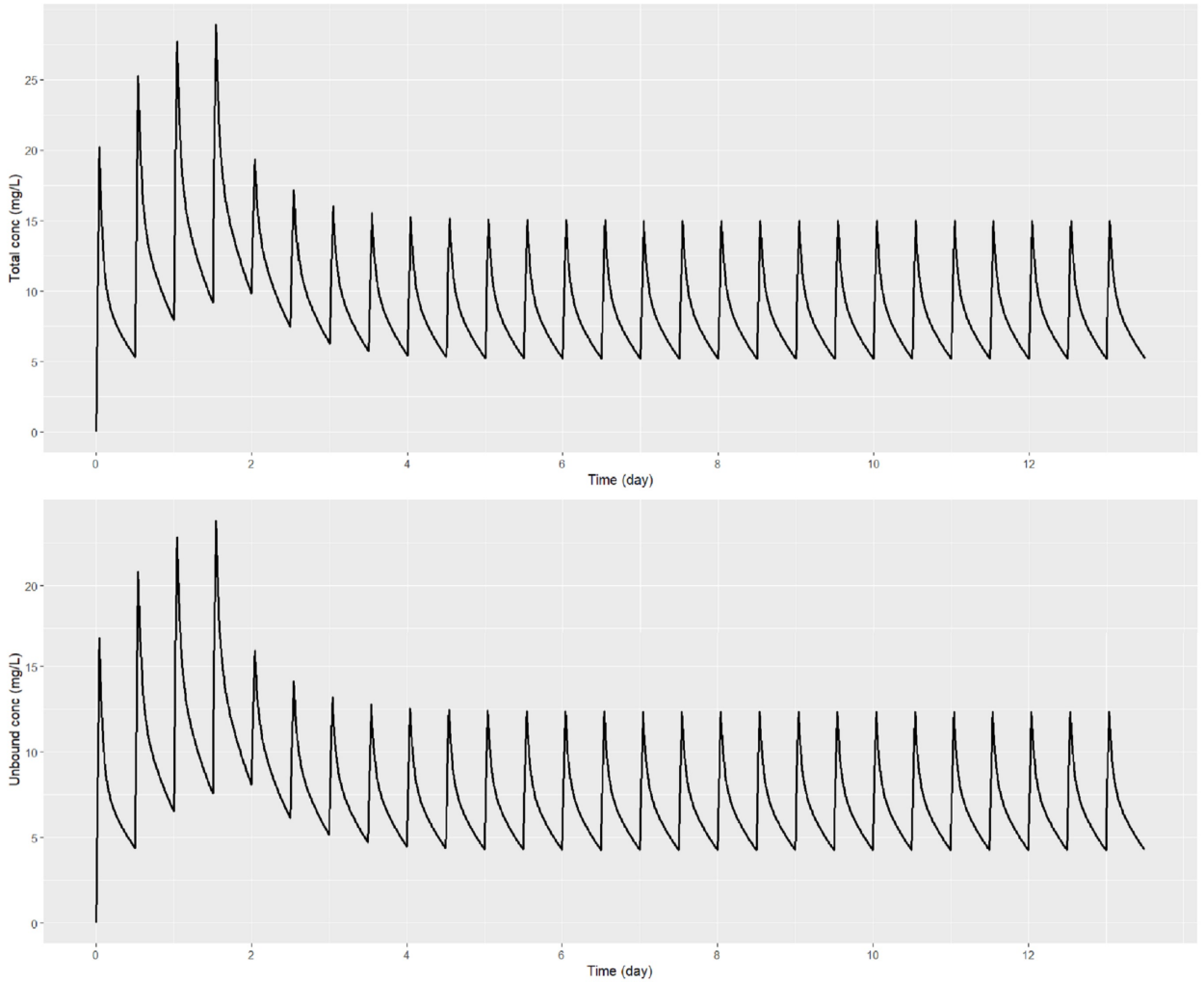


Figure 5

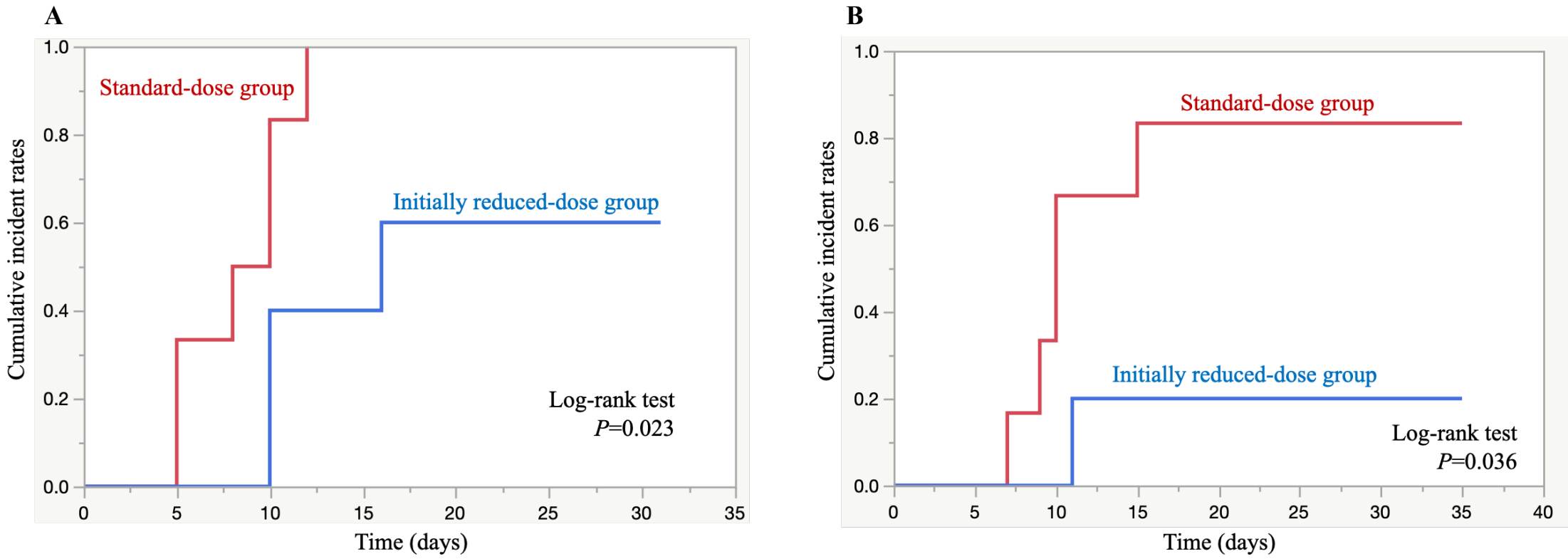
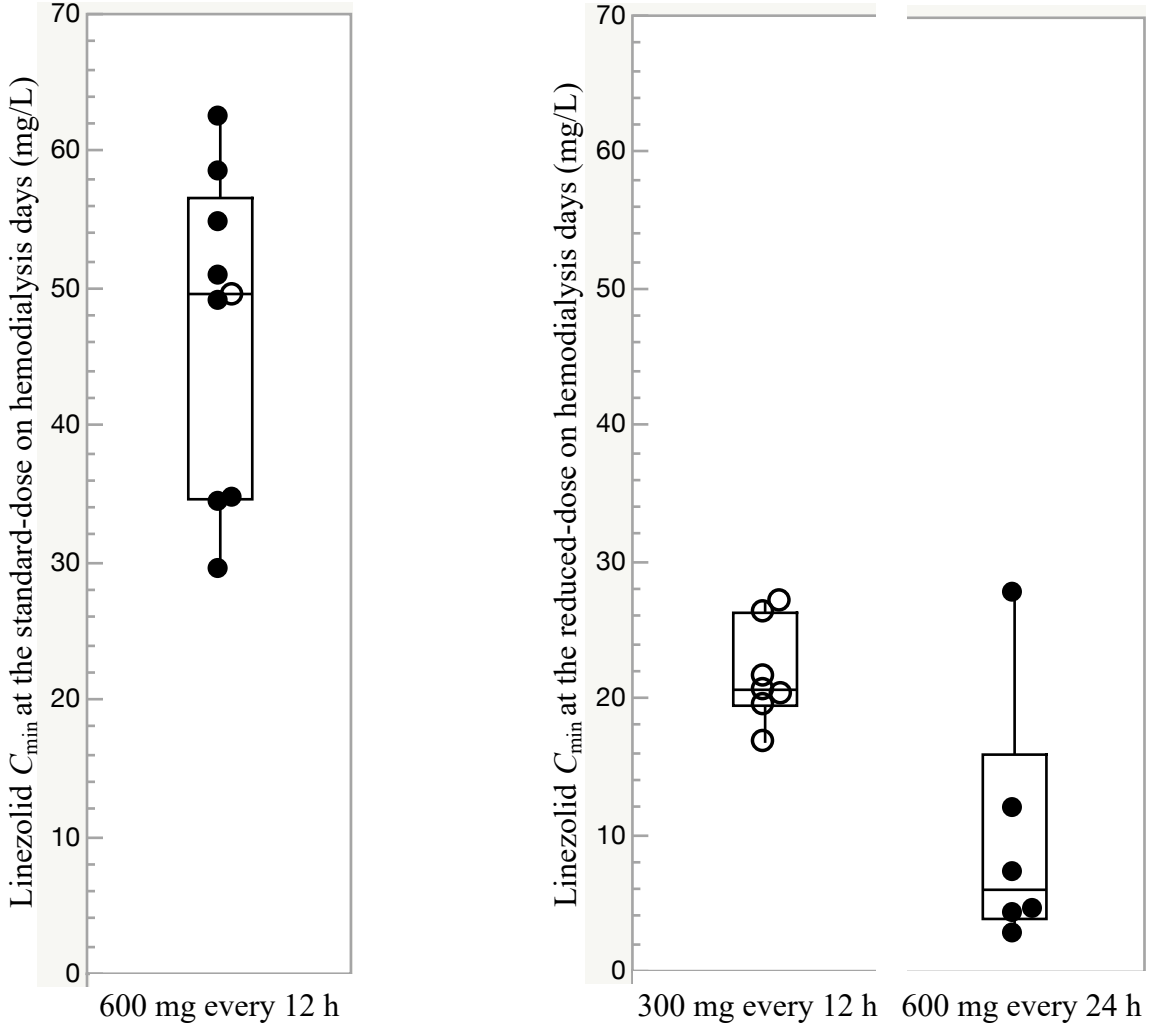
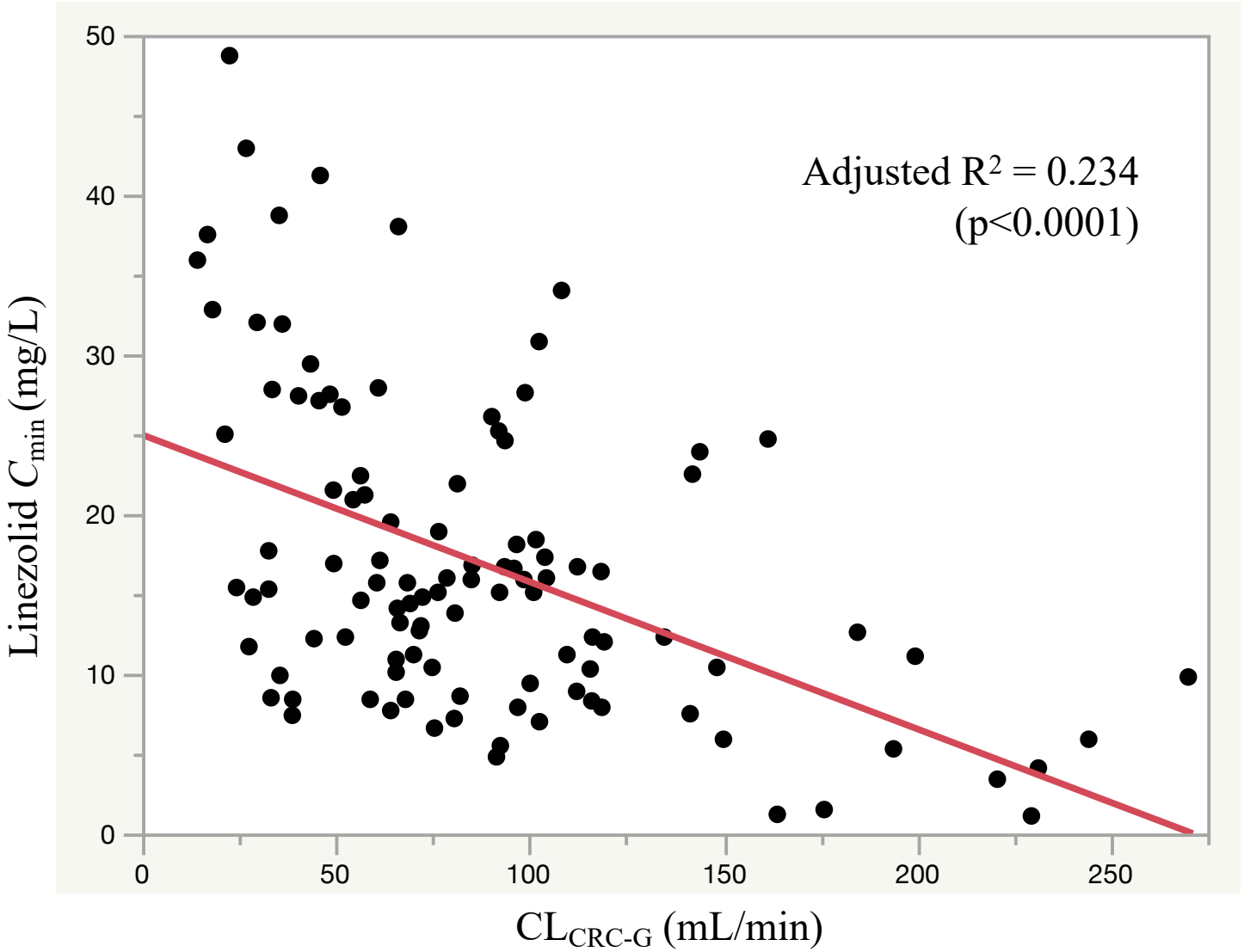

A
Cumulative incident rates
1.0
0.8
0.6
0.4
0.2
0.0
Standard-dose group
Initially reduced-dose group
Log-rank test
P=0.023
0
5
10
15
20
25
30
35
Time (days)
B
Cumulative incident rates
1.0
0.8
0.6
0.4
0.2
0.0
Standard-dose group
Initially reduced-dose group
Log-rank test
P=0.036
0
5
10
15
20
25
30
35
40
Time (days)

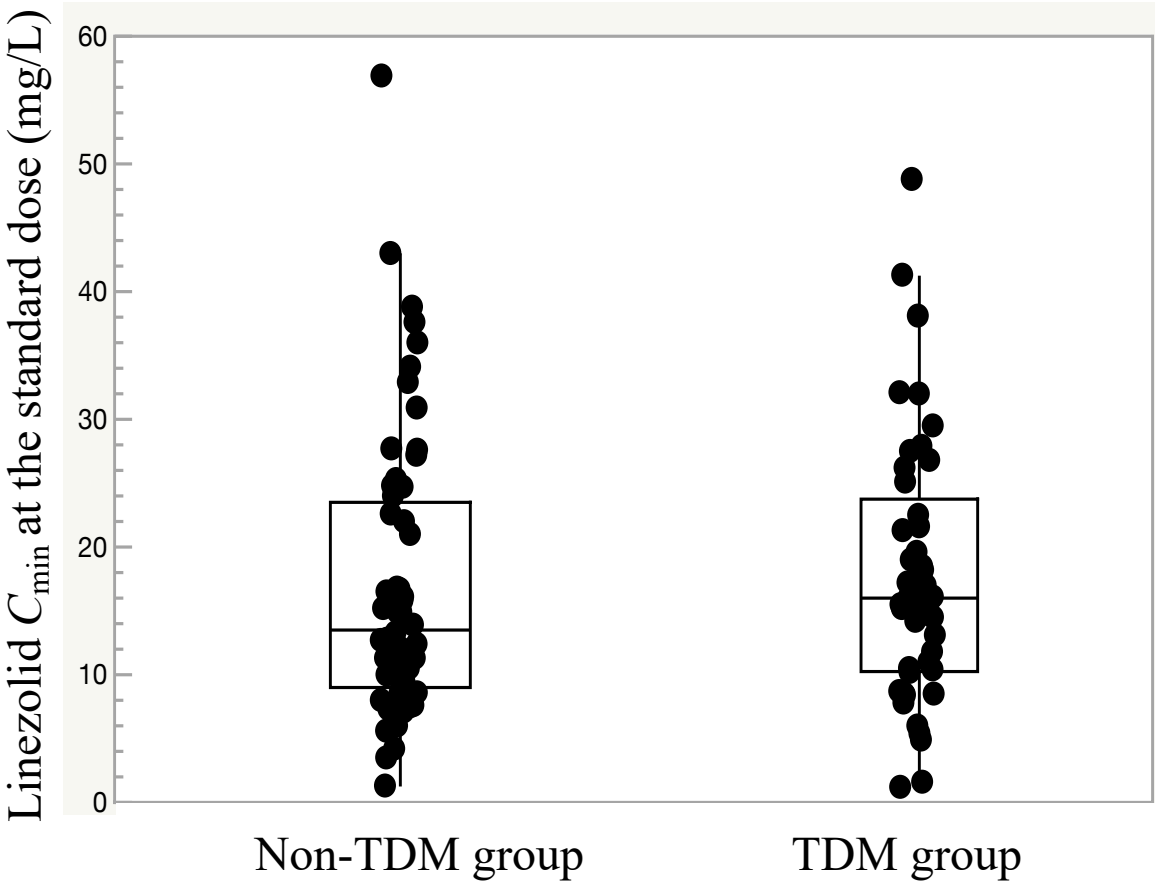
Figure 6


Linezolid C_{min} at the standard-dose on hemodialysis days (mg/L)
70
60
50
40
30
20
10
0
600 mg every 12 h
Linezolid C_{min} at the reduced-dose on hemodialysis days (mg/L)
70
60
50
40
30
20
10
0
300 mg every 12 h
600 mg every 24 h

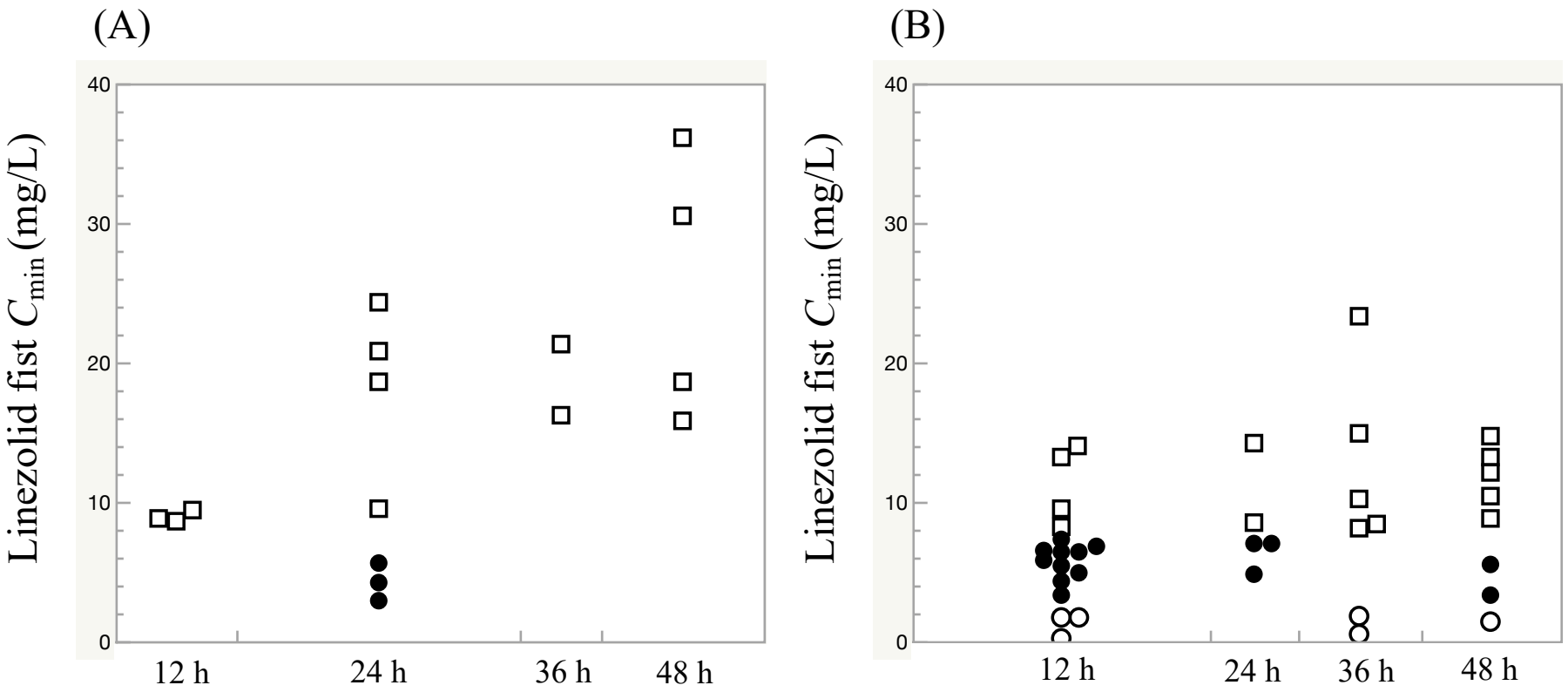
Supplemental Figure 1



Supplemental Figure 2



Supplemental Figure 3



The time after starting administration of fixed 600 mg every 12 h