



최저농도 기반 반코마이신 치료약물농도감시와 곡선아래면적 기반 반코마이신 치료약물농도감시 비교: 컴퓨터 시뮬레이션 연구

Comparison of Trough-Based and Area Under the Curve-Based Therapeutic Drug Monitoring of Vancomycin: An In Silico Study

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Background: Recent American guideline published in 2020 recommend using 24-h area under the curve (AUC)/minimum inhibitory concentration instead of vancomycin serum concentration (C_{trough}) for vancomycin therapeutic drug monitoring (TDM). However, C_{trough} -based TDM is widely used in clinical practice. Thus, this retrospective study aimed to compare C_{trough} -based and AUC-based TDM.

Methods: We evaluated patients' TDM data with at least one vancomycin trough measurement. Patients younger than 18 years, admitted to an intensive care unit, or on renal replacement therapy were excluded. The variables of C_{trough} -based and AUC-based TDM were simulated using Mw-Pharm++ (Mediware, Czech Republic) with vancomycin two-compartment model. The therapeutic range was 400-600 mg·h/L and 15-20 mg/L for AUC and C_{trough} , respectively. We evaluated the correlation between C_{trough} and AUC, the attainment rate of AUC target range, and changes in vancomycin dose and C_{trough} when AUC-based TDM is applied.

Results: One hundred and four patients were enrolled. C_{trough} and AUC correlated moderately ($R=0.707$, $P<0.001$). Among 31 patients with C_{trough} of 15-20 mg/L, the AUC of only 18 patients was within the target range (18/31, 58.1%). In addition, most patients with C_{trough} of 10-15 mg/L had the AUC within the target range (57/66, 86.4%). The respective vancomycin dose and C_{trough} were expected to be significantly lower in AUC-based TDM simulation than those in C_{trough} -based TDM simulation.

Conclusions: C_{trough} of 15-20 mg/L for vancomycin monitoring is not appropriate for attaining AUC target range. Targeting either AUC or lower C_{trough} is recommended for vancomycin TDM.

Key Words: Vancomycin, Therapeutic drug monitoring, Trough concentration, Area under the curve

INTRODUCTION

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Vancomycin is a glycopeptide antibiotic that inhibits bacterial cell wall synthesis by binding to the D-alanyl-D-alanine terminus of cell-wall precursors [1]. Due to its excellent antibiotic effect against gram-positive bacteria, vancomycin is used as the first-line therapy for methicillin-resistant *Staphylococcus aureus* (MRSA) infection, and other various indications including neutropenic fever, coagulase negative staphylococcus (CoNS), and other gram-positive bacterial infections [1]. However, since vancomycin has a narrow therapeutic index, therapeutic drug monitoring (TDM) is necessary for improving efficacy while preventing possible side effects, especially nephrotoxicity [2].

Since the release of the first consensus guideline on vancomycin monitoring, the 24-h AUC (AUC)/minimum inhibitory concentration (MIC) has been the primary pharmacokinetic (PK)/pharmacodynamic (PD) index. Nevertheless, serum vancomycin trough concentration (C_{trough}) has been suggested to be a surrogate monitoring index because it is easily available [2, 3]. However, the increase in vancomycin PK data raised concerns regarding C_{trough} use since C_{trough} greater than 15 mg/L frequently caused high AUC, which was associated with frequent vancomycin toxicity. Vancomycin TDM guidelines have been changed to reflect these new findings. The American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Pediatric Infectious Disease Society (PIDS), and the Society of Infectious Disease Pharmacists (SIDP) published a new consensus guideline in 2020 suggesting the use of AUC/MIC instead of C_{trough} for vancomycin monitoring in patients with serious MRSA infection [4]. Moreover, the revised guideline of the Chinese Pharmacological Society included the recommendation for monitoring AUC along with C_{trough} for vancomycin TDM [5].

However, due to the many drawbacks of AUC-based TDM, particularly the difficulty in obtaining AUC and unfamiliarity, many clinicians are still using C_{trough} for vancomycin monitoring. Surveys on the implementation and perceptions of vancomycin monitoring revealed that significant number of pharmacists, physicians, and institutions were unaware of the transition to AUC-based TDM or were not planning to adopt AUC-based TDM [6-9]. Therefore, intuitive investigation of the relationships between AUC and C_{trough} and the AUC attainment rate of C_{trough} -based TDM would help physicians use the adjusted TDM target in clinical practice.

This retrospective in silico study analyzed previous TDM data to assess the correlation between C_{trough} and AUC, the attainment rate of AUC target range, and the change in vancomycin dose based on a recent American guideline and the commonly used C_{trough} -based TDM in a Korean population.

MATERIALS AND METHODS

We evaluated the TDM data of patients who were referred for TDM consultation from April 1st, 2019, to April 30th, 2020, at the Department of Laboratory Medicine and Genetics, Samsung Medical Center Seoul, Korea. Patients with at least one vancomycin trough measurement were enrolled. Patients who were younger

than 18 years, admitted to an intensive care unit, or on renal replacement therapy were excluded. If patients were consulted multiple times during the given period, data from first TDM consultation were used for analysis. For impact analysis when transitioning to AUC-based TDM from trough-based TDM, C_{trough} data within 15-20 mg/L with the given regimen were included.

The following demographic characteristics, clinical information, and laboratory data were obtained for analysis and TDM: sex, age, height, body weight, diagnosis, vancomycin indication, vancomycin regimen, sampling time, serum vancomycin concentration, and serum creatinine. Creatinine clearance (CL_{Cr}) was calculated from serum creatinine concentration using Cockcroft-Gault equation. Vancomycin concentration was measured by the kinetic interaction of microparticles in solution immunoassay on Roche Cobas c702 analyzer (Roche, Basel, Switzerland). Based on our institution protocol, initial vancomycin measurements were performed prior to the third or fourth vancomycin injection. Follow-up vancomycin measurements, mostly prior to the third injection, were performed at the physician's discretion.

We used target AUC and C_{trough} ranges recommended by the American guidelines. The primary C_{trough} target range was established based on vancomycin indication: 15-20 mg/L for bacteremia, sepsis, pneumonia, catheter-related blood stream infection (CLABSI), central nervous system infection, and endocarditis, and 10-15 mg/L for neutropenic fever, skin infection, post-operative wound infection, otitis, and other non-complicated infections. The therapeutic range for AUC was 400-600 mg*h/L for serious MRSA infection and was extrapolated to other indications to explore the PK dynamics of vancomycin. The AUC attainment rate was defined as the proportion of patients with AUC within 400-600 mg*h/L divided by the total patients in the given C_{trough} target range. Similarly, the rate of failure to obtain AUC therapeutic range (failure rate) was defined as the proportion of patients who did not have AUC within the therapeutic range divided by the total patients in the given C_{trough} target range.

Estimated C_{trough} and AUC were calculated with commercial Bayesian PK software, MWPharm++ (MW) (Mediware, Praha, Czech Republic), using two-compartment vancomycin KKGIT (Dutch Association for Quality Assessment in TDM and Clinical Toxicology) population model [10]. The mean and standard deviation of PK fitting parameter were as follows: $C01.V$ (L/KgLBMc)= 0.21 ± 0.04 , $C02.kxy$ (1/h)= 1.12 ± 0.28 , $C02.kyx$ (1/h)= 0.48 ± 0.12 , and $RE.k$

$(1/\text{h}/(\text{mL}/\text{min}/1.73 \text{ m}^2)) = 0.00327 \pm 0.00109$. Patient covariates were age, sex, height, weight, and CL_{Cr} . For each patient, the recommended regimen for previous C_{trough} -based TDM consultations was simulated. The correlation between C_{trough} and AUC was evaluated, and the rate of failure to achieve AUC therapeutic range was calculated for C_{trough} target range with lower limit of 0-20 mg/L and range interval of 3.0 mg/L, 3.5 mg/L, 4.0 mg/L, 4.5 mg/L, and 5.0 mg/L. Furthermore, to investigate the expected changes in dose and trough when changing monitoring index from C_{trough} to AUC, additional analysis was performed on patients with C_{trough} of 15-20 mg/L. The doses needed to obtain AUC 400 mg*h/L (AUC400), 500 mg*h/L (AUC500), and 600 mg*h/L (AUC600) and the corresponding C_{trough} values were calculated.

MedCalc® version 77.5.1.0 (MedCalc Software Ltd., Ostend, Belgium) and IBM SPSS® Statistics version 25 (IBM Corp., Armonk, NY, USA) were used for statistical analyses. Pearson correlation analysis for estimated C_{trough} and AUC data from all enrolled patients was performed. Paired *t*-test and Wilcoxon signed rank test were performed to demonstrate statistically significant differences between C_{trough} and vancomycin dose of AUC-based TDM. A *P*-value less than 0.05 was considered statistically significant.

This study was approved by the Institutional Review Board (IRB) of Samsung Medical Center, Seoul, Korea (IRB number. SMC 2021-02-125-001), and the need for informed consent was waived.

RESULTS

The detailed characteristics of patients are described in Table 1. Vancomycin TDM data from 104 patients were available for correlation analysis between C_{trough} -based and AUC-based TDM. Under the C_{trough} -based recommended regimen, estimated C_{trough} was categorized into three groups: less than 10 mg/L (*n*=7), 10-15 mg/L (*n*=66), and 15-20 mg/L (*n*=31), as was estimated AUC: less than 400 mg*h/L (*n*=7), 400-600 mg*h/L (*n*=79), and 600 mg*h/L or more (*n*=18).

The AUC was within the therapeutic range in 18 of 31 patients with C_{trough} of 15-20 mg/L (18/31; attainment rate, 58.1%). On the other hand, 57 patients with C_{trough} of 10-15 mg/L had AUC within the therapeutic range (57/66; attainment rate, 86.4%). These results suggest that the AUC therapeutic range is difficult to obtain with the previously suggested target range of C_{trough} . Instead, a lower C_{trough} is needed to achieve the AUC therapeutic range. Pearson

Table 1. Patient characteristics

Parameter	Value
Age, years, mean \pm SD	56.89 \pm 17.22
\geq 65 yr, N (%)	66 (63.5)
< 65 yr, N (%)	38 (36.5)
Sex	
Male, N (%)	59 (56.7)
Female, N (%)	45 (43.3)
Weight, kg, median [IQR]	58.9 [52.9, 68.3]
Height, cm, mean \pm SD	164.01 \pm 9.63
BMI, kg/m ² , mean \pm SD	22.41 \pm 4.04
CL_{Cr} , mL/min/1.73 m ² , median [IQR]	97.7 [70.8, 126.2]
\geq 60 mL/min/1.73 m ² , N (%)	84 (80.8)
< 60 mL/min/1.73 m ² , N (%)	20 (19.2)
CL_{Cr} , mL/min median [IQR]	101.1 [74.7, 136.8]
\geq 60 mL/min, N (%)	86 (82.7)
< 60 mL/min, N (%)	18 (17.3)
Target vancomycin trough concentration*, N (%)	
10-15 mg/L	25 (34.0)
15-20 mg/L	79 (76.0)
Pathogen	
<i>Staphylococcus aureus</i>	19 (18.3)
MIC 1 mg/L	15 (78.9)
MIC \leq 0.5 mg/L	4 (21.1)
Coagulase negative <i>Staphylococcus</i>	13 (12.5)
MIC 2 mg/L	2 (15.4)
MIC 1 mg/L	7 (53.8)
MIC \leq 0.5 mg/L	4 (30.8)
<i>Enterococcus</i>	17 (16.3)
Vancomycin resistant <i>Enterococcus</i>	4 (3.8)
Vancomycin susceptible <i>Enterococcus</i>	13 (96.2)
Other gram positive bacteria	5 (4.8)
Gram negative bacteria	10 (9.6)
Not detected	40 (38.5)
Indication of vancomycin treatment, N (%)	
Bacteremia/Sepsis	35 (33.7)
Neutropenic fever	12 (11.5)
Pneumonia	10 (9.6)
Bone/joint infection	9 (8.7)
Post-operation wound infection	7 (6.7)
Intra-abdominal infection	6 (5.8)
Catheter related blood stream infection	5 (4.8)
CNS infection	5 (4.8)
Skin infection	3 (2.9)
Infectious endocarditis	2 (1.9)
Others	10 (9.6)
Total	104

Data are presented as mean \pm standard deviation, median (interquartile range), or number (percentage).

* Target vancomycin trough concentration was determined based on different indications. As additional clinical judgement was involved in previous consultation, there can be discrepancy between actual C_{trough} and target C_{trough} .

Abbreviations: BMI, body mass index; CL_{Cr} , creatinine clearance; CNS, central nervous system; MIC, minimum inhibitory concentration; N, number; SD, standard deviation; IQR, interquartile range.

correlation analysis revealed moderate correlation between estimated C_{trough} and AUC ($R=0.707$, $P<0.001$) (Fig. 1).

In estimating failure rate when using C_{trough} range, lower failure rates were observed at target ranges of 11.9 mg/L-14.9 mg/L, 11.0 mg/L-14.5 mg/L, 10.7 mg/L-14.7 mg/L, 10.2 mg/L-14.7 mg/L, and 9.5 mg/L-14.5 mg/L (Table 2). The upper limits of all suggested C_{trough} target ranges were near 15 mg/L, and the lower limits varied by range interval. Each candidate C_{trough} target range corresponded with AUC therapeutic range in 90% of patients.

Of the 104 patients, 31 met the 15-20 mg/L target based on pre-

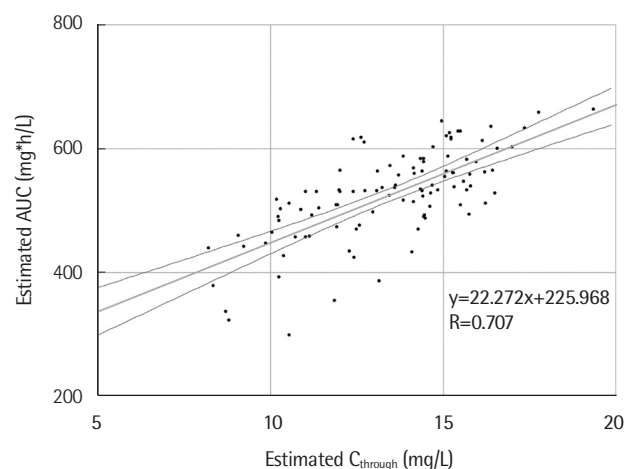
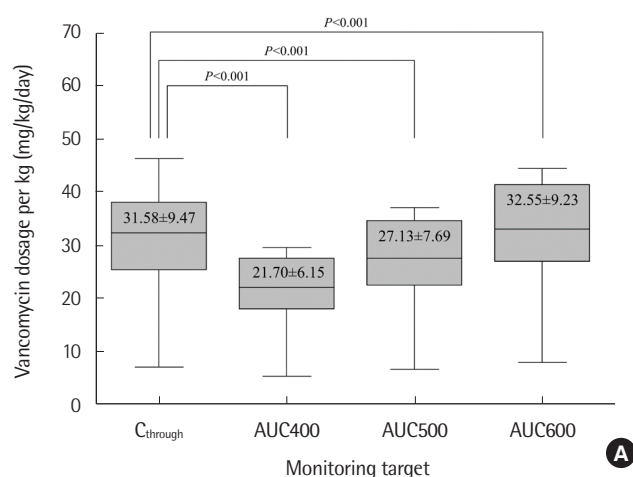


Fig. 1. Correlation between estimated C_{trough} and AUC ($N=104$). Regression line with 95% CI is shown.

Abbreviations: C_{trough} , serum vancomycin trough concentration; AUC, area under the curve for 24 h; CI, confidence interval.



vious TDM C_{trough} target. Among them, data from 28 patients were included for the assessment of change in vancomycin dose and C_{trough} when using AUC-based TDM. There were statistically significant decreases in both vancomycin dose and C_{trough} when targeting AUC 400 mg*h/L and 500 mg*h/L compared to the values when targeting C_{trough} of 15-20 mg/L (Fig. 2).

DISCUSSION

To the best of our knowledge, this is the first study comparing AUC-based and trough-based TDM using data from real clinical practices in Korean patients. In this retrospective study comparing C_{trough} -based TDM and AUC-based TDM, the achievement of

Table 2. Total failure rate, subtherapeutic AUC rate, and supratherapeutic AUC rate of candidate C_{trough} target range

Range interval (mg/L)	C_{trough} target range (mg/L)	Total failure rate (%)	Subtherapeutic AUC rate (%)	Supratherapeutic AUC rate (%)
3.0	11.9-14.9	10.6	2.1	8.5
3.5	11.0-14.5	10.2	4.1	6.1
4.0	10.7-14.7	9.3	3.7	5.6
4.5	10.2-14.7	11.5	6.6	4.9
5.0	9.5-14.5	11.5	6.6	4.9
2009 guideline	15.0-20.0	41.9	0.0	41.9

Abbreviations: Failure rate, rate of failure to attain AUC therapeutic range; C_{trough} , serum vancomycin trough concentration; AUC, area under the curve for 24 h. Total failure rate is the sum of subtherapeutic AUC rate plus supratherapeutic AUC rate.

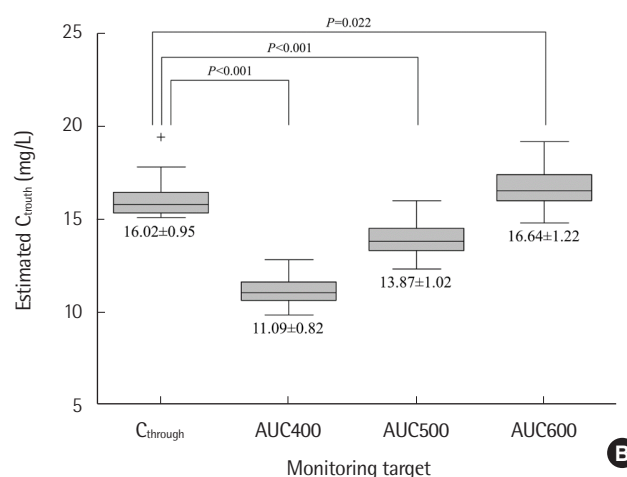


Fig. 2. Comparison of (A) vancomycin dosage per kg and (B) serum vancomycin trough concentration by monitoring target ($N=28$). The monitoring target is defined as follows: C_{trough} , serum vancomycin trough concentration of 15-20 mg/L; AUC400, AUC/MIC 400; AUC500, AUC/MIC 500; and AUC600, AUC/MIC 600, with MIC assumed to be 1 mg/L.

Abbreviations: AUC, area under the curve for 24 h; MIC, minimum inhibitory concentration; C_{trough} , serum vancomycin trough concentration.

target range and the correlation between C_{trough} and AUC were assessed in a Korean population. A moderate correlation was observed between AUC and C_{trough} . However, a considerable number of patients with C_{trough} of 15-20 mg/L were over-treated based on the recent AUC therapeutic range guidelines. Moreover, most patients with lower than recommended C_{trough} had an AUC therapeutic range of 400-600 mg*h/L. This unsatisfactory compatibility between C_{trough} target range and AUC target range was consistent with previous findings [4, 11-17]. Compared to trough-based TDM, AUC-based TDM was expected to achieve lower vancomycin dose and C_{trough} .

For AUC-based TDM, the revised American guideline has shown that lower vancomycin dosage could be adopted to prevent possible adverse effects of vancomycin, such as nephrotoxicity. The current American guideline based on several studies suggests an upper limit of AUC of 600 mg*h/L to prevent nephrotoxicity [4, 11, 18-21], and AUC-guided dosing based on this target range reduced nephrotoxicity without a significant increase in treatment failure compared to C_{trough} -based dosing [15, 20, 22-26]. Based on currently published data, adopting AUC-based TDM would help prevent unnecessary risk of nephrotoxicity.

However, not all institutions have access to Bayesian PK software, and some clinicians still use C_{trough} for vancomycin monitoring. Indeed, AUC is not intuitive as C_{trough} because it requires additional PK parameters and is derived from the calculation of such parameters. In the most recent survey conducted in 2020, 70% of responding clinicians answered that they had not implemented AUC-based TDM and 43.0% were not planning to adopt AUC-based TDM [6]. Therefore, although AUC-based TDM appears to be superior to trough-based TDM, alternative methods are needed to avoid the hesitancy associated with adopting AUC-based TDM. One option could be establishing an individual target C_{trough} based on the initial AUC calculation using the first-order PK equation and monitoring according to an established target C_{trough} range until significant conditional change occurs [27]. Further practical assessment and adjustment of vancomycin monitoring would be helpful.

Although this article mainly focused on the American guideline, the Chinese guideline does not discourage the use of C_{trough} for monitoring vancomycin. This might be because the Chinese guideline recommends a lower vancomycin C_{trough} lower limit (10 mg/L) and higher AUC upper limit (650 mg*h/L) for serious MRSA

infections compared to that recommended by the American guideline [3-5]. In this study, to assess whether simply lowering target C_{trough} is acceptable and explore the optimal target for C_{trough} range, we evaluated the rate of AUC therapeutic range attainment with lower vancomycin C_{trough} target range. Regardless of range interval, the upper limits of the optimal candidate ranges were near 15 mg/L, which is lower than the C_{trough} suggested by the 2009 American guideline. Considering this low failure rate, using lower target C_{trough} would be acceptable when AUC-based TDM is not conducted. However, further study is needed to determine if a low C_{trough} target yields the same clinical outcome as AUC-based TDM.

There are some limitations in this study. First, as this study was an in silico prediction, the comparison of clinical outcomes by TDM strategy was not performed. Moreover, when performing TDM simulation, we included all previous TDM consultation data including those with only one vancomycin measurement or non-steady state serum vancomycin concentration and real steady state C_{trough} could not be obtained. However, as stated in the current guideline and other studies, vancomycin TDM with the Bayesian approach can yield reliable prediction even with single non-steady state concentration [4, 28]. In addition, by simulating TDM as it is applied currently in practice, the data reflect real-world practice. Finally, this study was based on the assumption of AUC 400-600 mg*h/L as the accepted target range and assessed only PK factors affecting vancomycin administration. The actual applicability of AUC for indications other than serious MRSA infection, such as vancomycin-susceptible *Enterococcus* infection, was not addressed in this study. A further large-scale prospective study on the extrapolation of AUC target range is needed.

In conclusion, targeting C_{trough} of 15-20 mg/L is not appropriate for attaining the target AUC range and is associated with high AUC values. Using AUC-based TDM could result in a lower vancomycin dose. Applying a low C_{trough} might be acceptable, but further large study on the actual clinical outcomes is needed.

요 약

배경: 2020년 발표된 미국 가이드라인에서는 반코마이신 치료약 물농도감시(TDM)에 최저농도 대신 24시간 곡선아래면적(AUC)/최소억제농도를 이용할 것을 권고하였다. 하지만 아직도 실제 임상 환경에서는 최저농도 기반 TDM이 보편적으로 이용되고 있는 실정이다. 본 후향적 연구에서는 최저농도 기반 TDM과 AUC 기반

TDM을 비교평가 하고자 하였다.

방법: 1회 이상 반코마이신 최저농도를 측정한 환자들의 TDM 자료를 분석하였다. 18세 미만 환자와 중환자실 입원 환자, 신대체요법을 받고 있는 환자는 대상자에서 제외하였다. 최저농도 기반 TDM과 AUC 기반 TDM 시뮬레이션에는 MwPharm++ (Mediware, Czech Republic) 반코마이신 2 구획 모델을 이용하였다. AUC 및 최저농도의 치료목표범위는 각각 400-600 mg·h/L 및 15-20 mg/L로 정의하였다. 예측된 최저농도와 AUC의 상관관계, AUC 치료범위 달성률, 최저농도 대신 AUC 기반 TDM을 채택하였을 때의 반코마이신 용량 및 최저농도 변화를 분석하였다.

결과: 본 연구에는 총 104명 환자가 포함되었다. 예측된 최저농도와 AUC는 중등도의 상관관계를 보였다($R=0.707$, $P<0.001$). 최저농도가 15-20 mg/L인 31명 중 오직 18명만이 AUC 치료목표범위 이내인 반면(58.1%), 최저농도가 10-15 mg/L인 환자들의 대부분은 AUC 치료범위내에 포함되었다(86.4%). 또한, 치료목표를 최저농도 대신 AUC 기반으로 설정하여 시뮬레이션하는 경우에 반코마이신 투약용량 및 상응하는 최저농도가 의미 있게 낮았다.

결론: 최저농도 15-20 mg/L는 반코마이신 TDM에서 AUC 치료목표범위를 달성하기에 부적합하였다. AUC 또는 더 낮은 최저농도를 반코마이신 TDM의 치료목표로 적용할 필요성이 있을 것으로 생각된다.

Conflicts of Interest

None declared

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