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Tacrolimus IPV Group Membership Does Not Consistently Track With Electronically Monitored or Self-reported Adherence in Adolescent and Young Adult Kidney Transplant Recipients

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Background. High intrapatient variability (IPV) of tacrolimus trough concentrations (SD ≥ 2, coefficient of variation (CV%) ≥ 30) is associated with rejection and graft loss and may indicate nonadherence. However, the association between tacrolimus IPV and electronically monitored or self-reported adherence is unknown. **Methods.** This secondary analysis of the TAKE-IT (Teen Adherence in Kidney Transplant Effectiveness of Intervention Trial) compared electronically monitored and self-reported adherence between participants with high and low tacrolimus IPV among 103 adolescent and young adult kidney transplant recipients (mean age = 15.18 y, 59% male, 60% White, 65% >1-y posttransplant). **Results.** Electronically monitored daily taking and timing adherence were not significantly associated with tacrolimus IPV group in binomial generalized linear mixed effects models: Participants with tacrolimus SD ≥ 2 or CV% ≥ 30 were no less likely to take each daily dose than those below these cutoffs (SD < versus ≥ 2: odds ratio [OR]; 0.84, 95% confidence interval [CI], 0.48-1.47; $P = 0.54$ and CV% < versus ≥ 30: OR, 0.72; 95% CI, 0.43-1.21; $P = 0.22$). Participants with tacrolimus SD ≥ 2 or CV% ≥ 30 were no less likely to take each daily dose on time than those below these cutoffs (SD < versus ≥ 2: OR, 0.70; 95% CI, 0.40-1.23; $P = 0.21$ and CV% < versus ≥ 30: OR, 0.68; 95% CI, 0.40-1.16; $P = 0.15$). Electronically monitored averages of doses taken, doses taken early/late, and differences from expected dose time were associated with tacrolimus IPV ($P < 0.05$) but were poor classifiers of IPV group membership (area under the curve < 0.70). Self-reported adherence was not associated with tacrolimus IPV. **Conclusions.** Tacrolimus IPV group membership does not consistently track with behavioral adherence measures. Relying on tacrolimus IPV group membership may misidentify nonadherence in adolescent and young adult kidney transplant recipients.

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Adolescent and young adult kidney transplant recipients have the highest graft failure rates compared with younger and older individuals,[1-3] regardless of age at transplantation.[4] Immunosuppressant nonadherence rates are 2 times higher in this age group than in younger children, with 1-in-6 kidney graft losses attributed to nonadherence.[1,5] Effectively addressing immunosuppressant nonadherence could prevent rejection, graft loss, and death. However, accurately identifying inconsistent immunosuppressant medication-taking is an important antecedent to adherence-promoting intervention.

Tacrolimus intrapatient variability (IPV) based on trough concentrations from routine laboratory draws has been promoted as an objective measure of medication adherence,[6-8] with higher variability suggesting inconsistent medication ingestion.[6,9] Higher tacrolimus IPV is associated with important transplant outcomes, including rejection, graft loss, and the presence of donor specific antibodies in pediatric liver and kidney transplant recipients.[6,10-13] Specific cutoffs (SD ≥ 2,[6,9] coefficient of variation (CV%) ≥ 30) have been proposed to identify clinically important tacrolimus nonadherence in pediatric patients.[14] Tacrolimus IPV appears to be associated with negative graft outcomes[6,10-13] but it is unknown whether IPV is determined primarily by adherence behavior. Other factors may influence tacrolimus IPV, such as dose changes, drug interactions, blood draw frequency, taking with or without food, infections, and differences in drug metabolism possibly related to estrogen and other unique patient characteristics.[12,15,16]

Electronic medication adherence monitors (pillbox, pill bottle) and self-reported adherence tools are other methods of assessing medication adherence. Electronic adherence monitoring is regularly used in clinical research, often serving as the comparator for other adherence measures.[17] The date and time is recorded when the user opens/closes the device to take their medicine, providing an estimate of the timing, frequency, and regularity of medication administration. Self-reported adherence assessment tools (surveys, interviews) are low cost and commonly used in clinical settings.[18,19] However, both electronic monitoring and self-report are indirect as they do not record actual ingestion. Electronic monitoring may be measuring adherence to using the device and cannot guarantee medication was taken[20] or not taken (potentially administered from another source). Self-report is subject to recall and social desirability biases and may over-estimate adherence.[18,19]

Surprisingly little is known about how electronically monitored and self-reported adherence correlate with tacrolimus IPV during adolescence and young adulthood. Given that all 3 methods are purported to measure the same construct, electronically monitored and self-reported adherence should be strongly associated with tacrolimus IPV. Some evidence suggests tacrolimus IPV is associated with electronically monitored and self-reported adherence in pediatric kidney and liver transplant recipients[21-23] with effect sizes ranging from small for self-report and tacrolimus IPV[23] to medium[21] and large[22] for electronic monitoring and tacrolimus IPV. However, this prior research was limited by small sample sizes,[21,22] short assessment periods,[21,22] and wide age ranges that included younger children for whom caregivers play a large role in adherence.[21-23] Several studies of adult kidney transplant recipients demonstrated significant associations between self-report and tacrolimus IPV but no association between electronically monitored adherence and tacrolimus IPV.[24-27] Major limitations of this prior research are that adolescents and young adults have not been the age group of focus, despite evidence that this developmental stage is associated with lower adherence[1,5] as well as potential changes in tacrolimus metabolism[28] that could affect tacrolimus IPV relative to adherence.

The primary objective of this secondary analysis[29] of data collected from the TAKE-IT (Teen Adherence in Kidney Transplant Effectiveness of Intervention Trial) was to determine the association between tacrolimus IPV group membership (SD </≥ 2,[6] CV% </≥ 30[10,11]) and each of electronically monitored and self-reported adherence among adolescent and young adult kidney transplant recipients (11–24 y old) during a 12-mo observation phase. We hypothesized that participants with tacrolimus SD ≥ 2 and CV% ≥ 30 would have lower electronically monitored adherence and would be more likely to self-report nonadherence compared with participants with SD < 2 and CV% < 30. Because prior research on adolescent and young adult kidney transplant recipients showed higher electronically monitored and self-reported adherence in females than males but higher tacrolimus IPV in females than males,[16] we considered whether associations between tacrolimus IPV and adherence measured electronically and by self-report may differ by sex.

MATERIALS AND METHODS

Procedures

This is a secondary analysis of data collected in the multisite TAKE-IT trial; the primary results were previously reported.[29] TAKE-IT was approved by each participating sites' research ethics board (Research Ethics Board approval no. 10-365-PED). This secondary analysis was approved by the Johns Hopkins University School of Medicine Institutional Review Board (IRB00303550).

Briefly, TAKE-IT was a randomized controlled trial involving adolescents and young adults (11–24 y old) who underwent kidney transplantation at least 3 mo before enrollment and were followed at 1 of 8 participating transplant centers in Canada and the United States. The trial evaluated a multicomponent adherence-promoting intervention compared with a control group (detailed description in the primary TAKE-IT trial evaluation[29]). A 3-mo run-in phase (no intervention) was followed by a 12-mo intervention phase. Participants were asked to use an electronic multidose pillbox (e-pillbox) to measure medication adherence during the study. Self-reported adherence was assessed at study visits every 3 mo. Immunosuppressant medication trough concentrations were collected from participants' medical records throughout the trial.

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This secondary analysis focuses on tacrolimus trough concentrations, e-pillbox adherence, and self-reported adherence data from the 12-mo intervention phase for both randomized groups to reduce potential Hawthorne effects (behavior change in response to awareness that one is being observed)[30] that could influence electronically monitored adherence from introducing the e-pillbox during the run-in phase. It is also important to note that TAKE-IT enrolled participants taking any immunosuppressant medication. Given our interest in tacrolimus IPV, we excluded from this secondary analysis participants not prescribed tacrolimus.

Measures

E-Pillbox Adherence

Participants enrolled during the first 4–6 mo of recruitment used the MedMinder e-pillbox (MedMinder, Needham, MA). Because of technical difficulties with this device, participants enrolled during the remainder of the trial used the SimpleMed e-pillbox (Vaica Medical, Tel Aviv, Israel). Both devices recorded the date and time an e-pillbox compartment was opened/closed to administer medicine and automatically transmitted this timestamp to a secure web-based data collection platform. For this secondary analysis, electronically monitored adherence was measured for each participant as follows:

1. Primary e-pillbox outcomes: Daily taking and timing adherence. On each day of observation, daily taking adherence was scored as 1 if the participant took all expected daily tacrolimus doses and 0 if <100% of doses were taken as recorded by the e-pillbox. Daily timing adherence was scored as 1 if the participant took all expected daily tacrolimus doses <1 h before or <2 h after the expected time and 0 if <100% of doses were recorded as taken on time. No score was assigned on days the e-pillbox was turned off or not transmitting data. The repeated measures daily taking and timing adherence were selected as the primary e-pillbox outcomes to increase statistical power and to ensure appropriate weighting of observations contributed by participants with different durations of study participation. Each participant contributed as many daily adherence scores to the analysis as they had days of observation.
2. Secondary e-pillbox outcomes: E-pillbox adherence summary measures. Several adherence summary measures were calculated, consistent with how e-pillbox adherence data has traditionally been expressed as a single score summarizing adherence across the observation period for each individual.[31] This approach is simple, easy to understand, and commonly used but equally weights each participant's score in the analysis regardless of their observation length.
   a. Taken dose proportion was calculated as: (number of doses recorded on e-pillbox as taken within the observation period)/(number doses expected within the observation period based on the participant's dose schedule and the number of days of observation). Higher values reflect higher adherence.
   b. Early/late dose proportion was calculated as: (number of doses recorded on e-pillbox as taken >1 h before/after expected timing)/(number of doses recorded as taken on e-pillbox during the observation period). Higher values reflect higher nonadherence to dose timing. This metric reflects timing of doses recorded as taken and does not incorporate missed doses.
   c. Average difference from expected dose time (h) was calculated as the absolute value of the mean difference in time between doses recorded as taken during the observation period and the expected amount of time between doses based on tacrolimus schedule. For example, if a patient was prescribed tacrolimus twice-a-day, it was expected that the amount of time between doses would be 12 h. If the participant's average inter-dose interval was 14 h, the absolute difference of this number from the expected dosing gap was calculated as 14–12 h = 2 h. Higher values reflect greater inconsistency, on average, in dose administration timing.

Self-reported Adherence

Participants completed the Medication Adherence Measure[32] every 3 mo at study visits. Self-reported adherence during the 12-mo observation period was very high. Thus, this variable was dichotomized, as recommended in prior research (1 = any missed doses during observation period, 0 = no missed doses during observation period).[19]

Tacrolimus IPV

On a monthly basis per study protocol, research personnel extracted tacrolimus trough concentrations from clinical care, excluding values from hospitalizations or illnesses. Tacrolimus IPV was calculated for each participant with at least 3 trough concentrations occurring a minimum of >6 mo posttransplant and during the 12-mo monitoring phase.

Standard Deviation

The SD of all eligible trough concentrations was calculated for each participant and classified as SD < 2 or SD ≥ 2. A tacrolimus SD ≥ 2 was previously associated with acute rejection episodes and may reflect tacrolimus nonadherence.[6,9]

Coefficient of Variation

The CV% ([SD/mean] × 100) of all eligible tacrolimus trough concentrations was calculated and classified as CV% < 30 or CV% ≥ 30. Tacrolimus CV% ≥ 30 was associated with acute rejection episodes,[11] donor specific antibodies,[10] and may reflect tacrolimus nonadherence.

Patient Demographic and Clinical Characteristics

Demographic information (age at enrollment, sex, race, ethnicity, income) was recorded for all participants. Clinical characteristics (time since transplant, tacrolimus formulation, dose changes, viral infections, gastrointestinal infections, rejection episodes) during the observation phase were also captured.

Statistical Analysis

Participant demographic and clinical characteristics, e-pillbox adherence, self-reported adherence, and tacrolimus IPV were summarized descriptively as appropriate for continuous or categorical variables.

Binomial generalized linear mixed effects models[33] were used to compare daily taking and timing adherence (repeated measures) between those classified as tacrolimus SD < and SD ≥ 2 and by tacrolimus CV% < and CV% ≥ 30. The models included

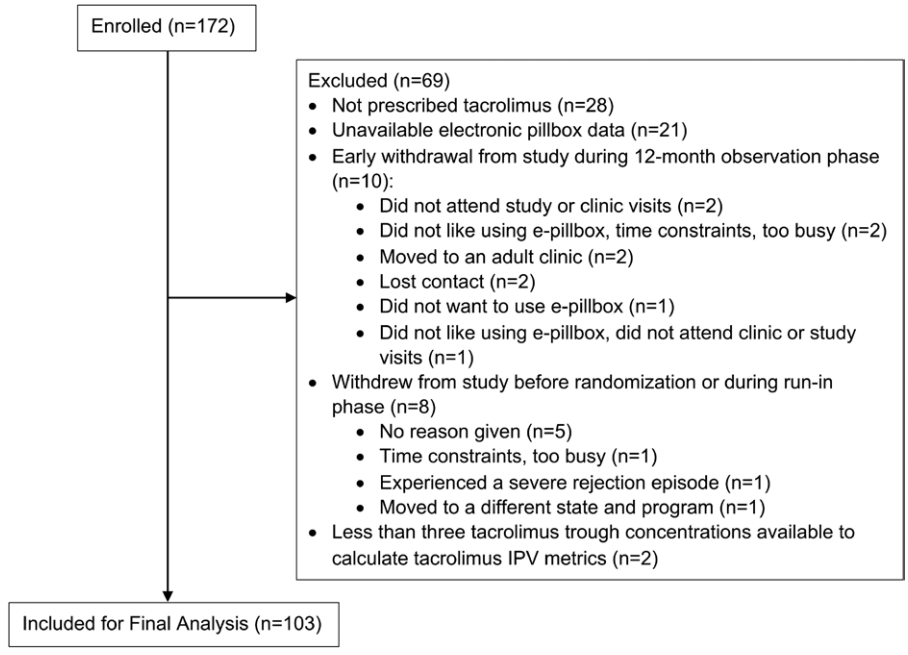

FIGURE 1. Study flow diagram of participant inclusion and exclusion for final analyzed sample. E-pillbox, electronic multidose pillbox; IPV, intrapatient variability.

a random effect for participant to account for repeated daily adherence. Randomization group was considered as a covariate but ultimately excluded as it does not function as a confounder in the relation between tacrolimus IPV group and electronically monitored or self-reported adherence.[34] Furthermore, these variables were hypothesized to measure the same construct, adherence, and, thus, were expected to be highly correlated under any conditions. Least squares means were generated for each tacrolimus IPV group (back transformed and bias adjusted based on the overall SD of the random effects).

Differences between groups classified by tacrolimus IPV in e-pillbox adherence summary measures were evaluated using Wilcoxon rank-sum tests and in classification as adherent or nonadherent by self-report were evaluated using chi-square tests. Before hypothesis testing, we evaluated variable distributions and found one participant's average difference from expected dose time represented extreme gaps in e-pillbox use; this metric was evaluated both including and excluding this participant's data.

Receiver operating characteristic (ROC) curve analyses were used to determine how well the e-pillbox adherence summary measures classified participants into tacrolimus IPV groups.[35] If the area under the curve (AUC) was <0.70, the adherence summary measure was considered a poor classifier of tacrolimus IPV group membership.

Given prior research suggesting that females may have higher tacrolimus IPV than males for reasons unrelated to adherence,[16] exploratory analyses were conducted stratified by sex.

A *P*-value of <0.05 was considered statistically significant. All analyses were conducted in RStudio 2024.04.2.

RESULTS

Participants

The TAKE-IT trial enrolled 172 participants. Based on inclusion/exclusion criteria for this secondary analysis, 69 (40%) were excluded as follows (Figure 1): not prescribed tacrolimus (n = 28, 41%), no e-pillbox data (n = 21, 30%), early withdrawal from the study during the 12-mo observation phase (n = 10, 14%), withdrew from the study before randomization or during the run-in phase (n = 8, 12%), and <3 eligible tacrolimus concentrations available to calculate tacrolimus IPV (n = 2, 3%).

This secondary analysis included 103 participants (mean age = 15.18 y, SD = 2.30), the majority of whom were male (59%), White (60%), non-Hispanic/Latino/a/x (89%), with a range of incomes represented. Just under half (47%) were randomized to TAKE-IT's intervention group. Detailed demographic information appears in Table 1.

Participant and medication regimen characteristics appear in Table 2. The majority of participants were >1-y posttransplant (65%; mean = 3.83 y, SD = 3.76) and took immediate release tacrolimus (86%). Half the sample had tacrolimus dose changes. While 25% experienced a viral infection, only 10% experienced a gastrointestinal infection. There were 11 participants who had a rejection episode. There were no graft losses.

Descriptive information on e-pillbox adherence, self-reported medication adherence, and tacrolimus IPV in the overall sample during the observation period appears in Table 3. The majority of participants self-reported no missed tacrolimus doses (78%). Based on the e-pillbox, participants, on average, took all of their daily doses (daily taking adherence) on 74% of the days observed (SD = 44%) and took all of their daily doses on time (daily timing adherence) on 67% of the days observed (SD = 47%). The median taken dose proportion was 69% (higher value = higher proportion of doses taken). The median early/late dose proportion was 44% (higher value = higher proportion of doses taken >1 h early or late). The median average difference from expected dose time was 4.43 h (higher value = higher difference in actual dose timing on average relative to expected dose timing).

TABLE 1.

Participant demographic characteristics

Overall sample	N = 103	SD < 2, n = 72	SD ≥ 2, n = 31	CV% < 30, n = 65	CV% ≥ 30, n = 38
Age, y, mean (SD)	15.18 (2.30)	15.17 (2.34)	15.21 (2.23)	15.11 (2.33)	15.30 (2.28)
Participant characteristics	N (%)	n (%)	n (%)	n (%)	n (%)
Sex					
Male	61 (59)	41 (57)	20 (65)	40 (62)	21 (55)
Race					
White	62 (60)	43 (60)	19 (61)	40 (62)	22 (58)
Black	12 (12)	6 (8)	6 (19)	4 (6)	8 (21)
Asian	11 (11)	8 (11)	3 (10)	9 (14)	2 (5)
American Indian	3 (3)	3 (4)	0	2 (3)	1 (3)
Native Hawaiian	3 (3)	2 (3)	1 (3)	1 (2)	2 (5)
More than 1 race	5 (5)	3 (4)	2 (6)	3 (5)	2 (5)
Not listed	7 (7)	7 (10)	0	6 (9)	1 (3)
Hispanic/Latino/a/x					
Yes	10 (10)	7 (10)	3 (10)	6 (9)	4 (11)
Not reported	1 (1)	1 (1)	0	1 (2)	0
Income					
<$25k	20 (19)	13 (18)	7 (23)	12 (18)	8 (21)
$25k–$50k	22 (21)	13 (18)	9 (29)	13 (20)	9 (24)
$51k–$75k	20 (19)	15 (21)	5 (16)	15 (23)	5 (13)
$76k–$100k	12 (12)	10 (14)	2 (6)	8 (12)	4 (11)
>$100k	18 (17)	13 (18)	5 (16)	10 (15)	8 (21)
Prefer not to answer	6 (6)	5 (7)	1 (3)	3 (5)	3 (8)
Not reported	5 (5)	3 (4)	2 (6)	4 (6)	1 (3)
TAKE-IT study group					
Intervention	48 (47)	30 (42)	18 (58)	25 (38)	23 (61)

Age (y) was calculated at the time of study enrollment.
CV%, coefficient of variation; TAKE-IT, Teen Adherence in Kidney Transplant Effectiveness of Intervention Trial.

TABLE 2.

Participant health and medication regimen characteristics

Participant characteristics	N (%), N = 103	SD < 2, n = 72	SD ≥ 2, n = 31	CV% < 30, n = 65	CV% ≥ 30, n = 38
>1-y posttransplant	67 (65)	50 (69)	17 (55)	43 (66)	24 (63)
Tacrolimus formulation					
Immediate release	89 (86)	60 (83)	29 (94)	53 (82)	36 (95)
Extended release	12 (12)	11 (15)	1 (3)	11 (17)	1 (3)
Switched during observation period	2 (2)	1 (1)	1 (3)	1 (2)	1 (3)
Tacrolimus dose change	51 (50)	34 (47)	17 (56)	30 (46)	21 (55)
Viral infections	26 (25)	18 (25)	8 (25)	16 (25)	10 (26)
Gastrointestinal infections	10 (10)	7 (10)	3 (9)	7 (11)	3 (8)
Rejection episodes	11 (11)	5 (7)	6 (19)	2 (3)	9 (23)

Time since transplantation was calculated from the date of transplantation to the baseline assessment date. Tacrolimus formulation and dose change, viral infections, gastrointestinal infections, and rejection episodes were measured during the 12-mo observation phase.
CV%, coefficient of variation.

The median tacrolimus SD was 1.36 and the median tacrolimus CV% was 25.63. Examination of tacrolimus IPV groups indicated that 30% had tacrolimus SD ≥ 2 and 37% had tacrolimus CV% ≥ 30.

Association Between E-Pillbox Adherence and Tacrolimus IPV

Primary Outcomes: Repeated Measures Daily Taking and Timing Adherence

In the overall sample examining associations between e-pillbox adherence and tacrolimus SD, daily taking adherence was 100% on 71% of days among participants with SD < 2 compared with 68% of days among those with SD ≥ 2. The likelihood of taking all daily doses was lower for those with tacrolimus SD ≥ 2 than those with SD < 2 (odds ratio [OR], 0.84; 95% confidence interval [CI], 0.48-1.47; $P = 0.54$) but the CI was wide and the difference was not statistically significant. Daily timing adherence was 100% on 64% of the days among participants with SD < 2 compared with 58% of days among those with SD ≥ 2. The likelihood of taking all daily doses on time was lower for those with tacrolimus SD ≥ 2 than those with SD < 2 (OR, 0.70; 95% CI, 0.40-1.23; $P = 0.21$) but the CI was wide and the difference was not statistically significant.

Similarly, while those with tacrolimus CV% ≥ 30 had a lower likelihood of taking all daily doses and of taking all

TABLE 3.

E-pillbox daily adherence and adherence summary measures, self-reported adherence, and tacrolimus intrapatient variability during the observation phase

E-pillbox daily adherence	Mean (SD)
Daily taking adherence	0.74 (0.44)
Daily timing adherence	0.67 (0.47)
E-pillbox adherence summary measures	Median (IQR)
Taken dose proportion	0.69 (0.46–0.80)
Early/late dose proportion	0.44 (0.27–0.69)
Average difference from expected dose time (h)	4.43 (2.67–10.26)
Self-reported adherence	N (%)
Any missed	23 (22)
Tacrolimus intrapatient variability	Median (IQR)
SD	1.36 (0.96–2.09)
Coefficient of variation %	25.63 (19.63–35.36)
Tacrolimus intrapatient variability groups	N (%)
SD ≥ 2	31 (30)
Coefficient of variation % ≥ 30	38 (37)

Higher daily adherence score and taken dose proportion reflect higher adherence. Higher early/late dose proportion and average difference from expected dose time (h) reflect higher nonadherence (higher degree of late or early doses).
E-pillbox, electronic multidose pillbox; IQR, interquartile range.

daily doses on time than those with CV% < 30, the CIs were wide and the differences were not statistically significant. Specifically, daily taking adherence was 100% on 72% of days among participants with CV% < 30 compared with 67% with CV% ≥ 30. The likelihood of taking all daily doses was lower for those with tacrolimus CV% ≥ 30 than those with CV% < 30 (OR, 0.72; 95% CI, 0.43-1.21; $P = 0.22$) but the difference was not statistically significant. Daily timing adherence was 100% on 65% of days among participants with CV% < 30 compared with 58% with CV% ≥ 30. The likelihood of taking all daily doses on time was lower for those with tacrolimus CV% ≥ 30 than those with CV% < 30 (OR, 0.68; 95% CI, 0.40-1.16; $P = 0.15$) but the difference was not statistically significant. See Tables 4 and 5 for details.

Exploratory Analysis Stratified by Sex

Males

The likelihood of taking all daily doses was lower for male participants with tacrolimus SD ≥ 2 than those with SD < 2 (OR, 0.67; 95% CI, 0.31-1.43; $P = 0.30$) but the CI was wide and the difference was not statistically significant. Similarly, the likelihood of taking all daily doses on time was lower for male participants with SD ≥ 2 than those with SD < 2 (OR, 0.51; 95% CI, 0.24-1.11; $P = 0.09$) but the CI was wide and the difference was not statistically significant.

The likelihood of taking all daily doses was lower for male participants with tacrolimus CV% ≥ 30 than those with CV% < 30 (OR, 0.64; 95% CI, 0.30-1.35; $P = 0.24$) but the CI was wide and the difference was not statistically significant. Similarly, the likelihood of taking all daily doses on time was lower for male participants with CV% ≥ 30 than those with CV% < 30 (OR, 0.63; 95% CI, 0.29-1.35; $P = 0.24$) but the CI was wide and the difference was not statistically significant. See Tables 4 and 5 for details.

Females

The likelihood of taking all daily doses was higher for female participants with tacrolimus SD ≥ 2 than those with SD < 2 (OR, 1.12; 95% CI, 0.51-2.46; $P = 0.78$) but the CI was wide and the difference was not statistically significant. Similarly, the likelihood of taking all daily doses on time was higher for those with SD ≥ 2 than those with SD < 2 (OR, 1.10; 95% CI, 0.51-2.39; $P = 0.81$) but the CI was wide and the difference was not statistically significant.

The likelihood of taking all daily doses was lower for female participants with tacrolimus CV% ≥ 30 than those with CV% < 30 (OR, 0.87; 95% CI, 0.43-1.75; $P = 0.69$) but the CI was wide and the difference was not statistically significant. Similarly, the likelihood of taking all daily doses on time was lower for those with CV% ≥ 30 than those with CV% < 30 (OR, 0.76; 95% CI, 0.38-1.52; $P = 0.43$) but the CI was wide and the difference was not statistically significant. See Tables 4 and 5 for details.

Secondary Outcomes: E-Pillbox Adherence Summary Measures and Self-reported Adherence

Participants with tacrolimus SD ≥ 2 had significantly lower taken dose proportions, higher early/late dose proportions, and higher average difference from expected dose time compared with those with SD < 2. Average difference from expected dose time remained significantly higher among

TABLE 4.

E-pillbox and self-reported adherence by tacrolimus intrapatient SD

	Overall sample		Males		Females	
E-pillbox and self-reported adherence	**SD < 2 (n = 72, 70%)**	**SD ≥ 2 (n = 31, 30%)**	**SD < 2 (n = 41, 67%)**	**SD ≥ 2 (n = 20, 33%)**	**SD < 2 (n = 31, 74%)**	**SD ≥ 2 (n = 11, 26%)**
E-pillbox daily adherence, least squares mean (SE)						
Taking adherence	0.71 (0.03)	0.68 (0.04)	0.74 (0.04)	0.68 (0.05)	0.68 (0.04)	0.70 (0.06)
Timing adherence	0.64 (0.03)	0.58 (0.04)	0.66 (0.04)	0.56 (0.04)	0.61 (0.04)	0.63 (0.06)
E-pillbox summary measures, median (IQR)						
Taken dose proportion	0.73 (0.49–0.81)	0.56 (0.34–0.78)[a]	0.74 (0.49–0.81)	0.54 (0.34–0.77)[a]	0.69 (0.52–0.82)	0.63 (0.35–0.80)[a]
Early/late dose proportion	0.41 (0.27–0.66)	0.51 (0.26–0.74)[a]	0.47 (0.30–0.65)	0.60 (0.42–0.74)[a]	0.40 (0.26–0.70)	0.27 (0.19–0.65)[a]
Average difference from expected dose time (h)	3.85 (2.56–7.53)	6.30 (2.92–18.82)[a]	3.52 (2.58–6.94)	8.06 (3.23–18.20)[a]	5.41 (2.59–8.57)	4.04 (2.79–18.09)[a]
Self-reported adherence, n (%)						
Any missed tacrolimus dose(s)	18 (25)	5 (16)	8 (20)	4 (20)	10 (32)	1 (9)

Higher daily adherence score and taken dose proportion reflect higher adherence. Higher early/late dose proportion and average difference from expected dose time (h) reflect higher nonadherence (higher degree of late or early doses).
[a]$P < 0.05$.
E-pillbox, electronic multidose pillbox; IQR, interquartile range.

TABLE 5.

E-pillbox and self-reported adherence by tacrolimus intrapatient coefficient of variation %

	Overall sample		Males		Females	
E-pillbox and self-reported adherence	**CV% < 30 (n = 65, 63%)**	**CV% ≥ 30 (n = 38, 37%)**	**CV% < 30 (n = 40, 66%)**	**CV% ≥ 30 (n = 21, 34%)**	**CV% < 30 (n = 25, 60%)**	**CV% ≥ 30 (n = 17, 40%)**
E-pillbox daily adherence, least squares mean (SE)						
Taking adherence	0.72 (0.03)	0.67 (0.04)	0.75 (0.04)	0.67 (0.05)	0.69 (0.04)	0.67 (0.05)
Timing adherence	0.65 (0.03)	0.58 (0.03)	0.65 (0.04)	0.58 (0.05)	0.64 (0.04)	0.59 (0.05)
E-pillbox summary measures, median (IQR)						
Taken dose proportion	0.74 (0.56-0.85)	0.52 (0.33-0.78)[a]	0.74 (0.53-0.82)	0.51 (0.35-0.77)[a]	0.72 (0.58-0.85)	0.56 (0.27-0.78)[a]
Early/late dose proportion	0.42 (0.27-0.66)	0.49 (0.27-0.73)[a]	0.49 (0.33-0.65)	0.57 (0.30-0.73)[a]	0.33 (0.23-0.67)	0.41 (0.26-0.73)[a]
Average difference from expected dose time (h)	3.56 (2.63-7.39)	6.23 (2.76-16.98)[a]	3.85 (2.69-7.64)	6.30 (2.74-17.35)[a]	3.53 (2.22-6.84)	6.16 (3.01-15.89)[a]
Self-reported adherence, n (%)						
Any missed tacrolimus dose(s)	13 (20)	10 (26)	7 (18)	5 (24)	6 (24)	5 (29)

Higher daily adherence score and taken dose proportion reflect higher adherence. Higher early/late dose proportion and average difference from expected dose time (h) reflect higher nonadherence (higher degree of late or early doses).

[a]$P < 0.05$.

CV%, coefficient of variation; E-pillbox, electronic multidose pillbox; IQR, interquartile range.

participants with tacrolimus SD ≥ 2 and compared with those with SD < 2, even after excluding the outlier.

Similarly, participants with tacrolimus CV% ≥ 30 had significantly lower taken dose proportions, higher early/late dose proportions, and higher average difference from expected dose time compared with those with CV% < 30. Average difference from expected dose time remained significantly higher among participants with tacrolimus CV% ≥ 30 compared with those with CV% < 30, even after excluding the outlier.

Visualizations of individual e-pillbox adherence summary scores datapoints and box plots within each tacrolimus IPV group appear in Figure 2 and in **Figure S1** (**SDC**, https://links.lww.com/TXD/A762). There were no significant differences in the proportion of participants classified as adherent by self-report between tacrolimus IPV groups. See Tables 4 and 5 for details.

Classification of Tacrolimus IPV Group

We examined how well e-pillbox summary measures classified participants into IPV groups using ROC curve analyses. The AUC for taken dose proportion was 0.63 in relation to tacrolimus SD </≥ 2 and 0.69 in relation to CV% </≥ 30. The AUC for early/late dose proportion was 0.54 in relation to tacrolimus SD </≥ 2 and 0.52 in relation to CV% </≥ 30. The AUC for average difference from expected dose time was 0.62 in relation to tacrolimus SD </≥ 2 and 0.61 in relation to CV% </≥ 30. All AUCs were <0.70, indicating that e-pillbox adherence summary measures were poor classifiers of tacrolimus IPV group.

Sex-stratified Analyses

Male participants with tacrolimus SD ≥ 2 had significantly lower taken dose proportions, higher early/late dose proportions, and higher average difference from expected dose time compared with males with SD < 2. Similarly, male participants with tacrolimus CV% ≥ 30 had significantly lower taken dose proportions, higher early/late dose proportions, and higher average difference from expected dose time compared with males with CV% < 30. See Tables 4 and 5 for details.

Female participants with tacrolimus SD ≥ 2 had significantly lower taken dose proportions but had lower early/late dose proportions and smaller average difference from expected dose time compared with females with SD < 2. Female participants with tacrolimus CV% ≥ 30 had significantly lower taken dose proportions and higher early/late dose proportions and larger average difference from expected dose time compared with females with CV < 30. See Tables 4 and 5 for details.

There were no significant differences in the proportion of participants classified as adherent by self-report between tacrolimus IPV groups (Tables 4 and 5).

DISCUSSION

Adolescent and young adult kidney transplant recipients have high rates of medication nonadherence,[1] a risk factor for graft loss.[1,5] High tacrolimus IPV is also predictive of poor transplant outcomes.[6,10,11] In the current sample, tacrolimus IPV and e-pillbox adherence were suboptimal: about one-third of participants were above tacrolimus IPV cutoffs (SD ≥ 2, CV% ≥ 30) and <80% of doses were recorded as taken based on the e-pillbox. There is no gold standard for measuring adherence and every method, including electronic monitoring, has limitations. However, one would expect that different methods of measuring adherence should at least be correlated since they aim to measure the same construct.

The primary outcomes, repeated measures of daily taking and timing adherence, showed no significant association between electronically monitored adherence and tacrolimus IPV. The point estimates suggest that poorer electronically monitored adherence may be associated with higher tacrolimus IPV, but the association was not statistically significant. This may be because of the relatively small sample size and high variability. It is possible that differences exist that could not be detected. However, analysis of repeated daily adherence measures provides more power than any other methods we used. Importantly, tacrolimus IPV is a summary metric

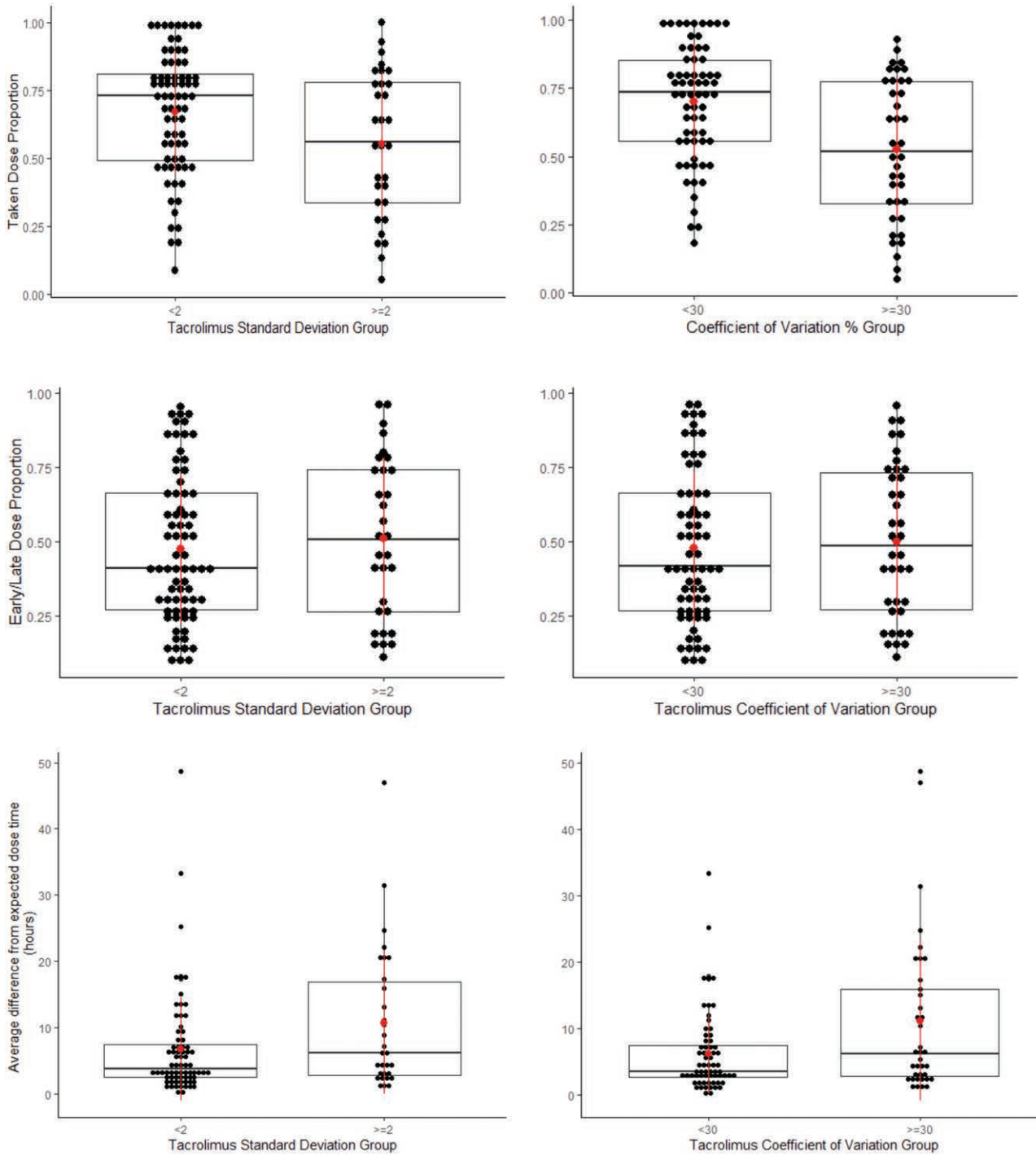

FIGURE 2. Dot plot with overlaid box plot of electronic multidose pillbox (E-pillbox) adherence summary measures (y-axis) and tacrolimus intrapatient variability groups (x-axis). The taken dose proportion and early/late dose proportion box plots visualize the overall sample (N = 103). Average difference from expected dose time box plot excludes the single outlier to aid in visual interpretation (n = 102).

derived from individual drug concentration values often taken 3 or more months apart, with potential variability introduced from blood draw timing relative to dosing; each level reflects medication ingestion in the few days before the blood draw. Tacrolimus IPV may be sensitive to extreme, chronic variability in medication administration and, particularly, nonadherence in the days leading up to the blood draw. Occasional missed or late doses recorded on an e-pillbox may not lead to high variability in tacrolimus levels and high variability in tacrolimus levels may not indicate problems with missed or late doses. It is important to note that electronic monitoring may not always accurately reflect behavior. Participants may open the device without ingesting the medication, or, perhaps more likely, take the medication from a source other than the device.

Using e-pillbox adherence summary measures, we showed significant associations between electronically monitored adherence and tacrolimus IPV. This finding is consistent with

prior pediatric transplant studies examining similar electronically monitored adherence summary scores in relation to tacrolimus IPV.[21,22] The fact that tacrolimus IPV was significantly associated with adherence assessed using methods that overweight the contributions of participants with fewer days of observation may reflect a tendency for patients with poorer adherence to drop-out of observation early. However, ROC curve analyses indicated that adherence based on e-pillbox summary measures was a poor classifier of tacrolimus IPV group membership. This finding is consistent with our primary outcome results that high tacrolimus IPV does not consistently track with poor e-pillbox adherence: some people with higher e-pillbox adherence will have higher tacrolimus IPV, and some people with lower e-pillbox adherence will have lower tacrolimus IPV.

Consistent with prior research involving adolescents and young adults with solid organ transplant,[36] self-reported tacrolimus adherence in this study was high. This likely reflects the short reference period ("the past 7 d") assessed using the Medication Adherence Measure,[32] at least in part. The tendency to report perfect adherence across 12 mo likely reduced our ability to find differences in self-reported adherence by tacrolimus IPV group. Self-reporting adherence over a longer reference period may yield more representative information.[19]

Our exploratory analyses stratified by sex showed that, among females, tacrolimus SD ≥ 2 was associated with significantly lower early/late dose proportions and average difference form expected dose time compared with SD < 2 (opposite direction from the overall sample and males). Similarly, ORs suggested that females with tacrolimus SD ≥ 2 had a higher likelihood of daily taking and timing adherence compared with SD < 2 (opposite direction from the overall sample and males), although these estimates were uncertain, with wide CIs. These hypothesis generating results are limited by sample size but add to preliminary evidence that tacrolimus IPV may be more variable in female adolescent and young adult kidney transplant recipients compared with males despite better behavioral adherence.[16] Research with larger samples is needed to confirm how sex is related to tacrolimus IPV.

LIMITATIONS

While the sample size was larger than in prior studies,[21,22] some participants were excluded primarily for taking an immunosuppressant other than tacrolimus (impossible to calculate tacrolimus IPV) or absent e-pillbox data, underscoring challenges with using tacrolimus IPV in clinical settings as not all kidney transplant recipients take tacrolimus, as well as with introducing e-pillboxes into patients' existing routines. However, the association between tacrolimus IPV and electronically monitored adherence is not expected to systematically differ between individuals with e-pillbox data and those without; tacrolimus IPV and electronic monitoring are both intended to measure adherence. This study was not designed to evaluate tacrolimus IPV, e-pillbox adherence, or self-reported adherence in relation to rejection episodes or graft loss, tacrolimus formulation, or patient characteristics beyond sex differences, although these are important future directions. We relied on commonly used tacrolimus IPV cutoffs, SD ≥ 2[6] and CV% ≥ 30,[10,11] and SD ≥ 2 has primarily been used with pediatric liver transplant patients;[6] other cutoffs may have yielded different results. Importantly, regardless of the condition for which tacrolimus is prescribed, this medication's pharmacokinetics and pharmacodynamics are the same.

IMPLICATIONS AND FUTURE RESEARCH

In this study of adolescent and young adult kidney transplant recipients, tacrolimus IPV was not significantly associated with e-pillbox daily taking or timing adherence or self-reported adherence. Although tacrolimus IPV was significantly associated with e-pillbox adherence summary measures, these measures were poor classifiers of tacrolimus IPV categories associated with negative clinical outcomes.[6,10-13] Thus, reliance on tacrolimus IPV to evaluate adherence in adolescent and young adult kidney transplant recipients may be misleading. Much of the prior pediatric research on tacrolimus IPV was conducted in liver transplantation, and included younger children.[6,9] The lack of association between tacrolimus IPV and electronically measured adherence among adolescent and young adult kidney transplant recipients may be due, at least in part, to more variable ingestion with food in this age group, which could affect tacrolimus pharmakinetics,[37] or variability in tacrolimus metabolism related to estrogen levels in post-menarchal girls.[16] However, our findings suggest that reasons other than nonadherence should be sought in the face of a high tacrolimus IPV in adolescent and young adult kidney transplant recipients. Alternatively, a low tacrolimus IPV is not a guarantee of good adherence.

Nonadherence is a complex behavior that likely requires a multimethod approach to assess accurately. Incorporating as many information sources as available, rather than relying on a single standalone measure of adherence, will likely provide the best clinical picture of a patient's adherence and health. This includes investigating alternative explanations for high tacrolimus IPV and interpreting adherence behavior in the context of patients' transplant and health outcomes.

Further investigation is warranted to continue building our understanding of how tacrolimus IPV relates to e-pillbox and self-reported adherence in adolescent and young adult kidney transplant recipients, especially considering the well-known risk for poor adherence[1,5] and high graft failure rates[1-4] during this critical developmental period. Other future directions include evaluating how to most effectively use existing tools and developing new tools to accurately measure adherence in adolescent and young adult kidney transplant recipients, in addition to determining how behavioral adherence measures are associated with poor transplant outcomes.

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