**SUPPLEMENT**

**EXPANDED RESULTS Fittings:** The fitted parameters (CL, V1, CL12 or CL21 and V2) for each CRD stage and risk groups are summarized in Table 2. Total TXA plasma clearance (CL) was found to be significantly decreased with increased severity of CRD (from stages 1 to 5). Although there was no trend for the volume of distribution of the central compartment (V1) among the low risk stages 1-5, differences were observed between the low vs. high risk groups for each of the stages. The V1 for the high risk group was 17 to 68% those for the corresponding low risk group (Table 2). Although changes in the volume of distribution in peripheral compartment (V2) were not significantly different, notable differences were observed between two risk groups (Table 2). The inter-compartmental clearances (CL12 and CL21) were significantly different among 5 stages of CRD, and between the two risk groups, likely due to changes in hemodynamics between the groups. These fitted results suggest the CRD stage and risk group are potential covariates responsible for inter-subject variability in TXA disposition. To further study covariate effects, population modelling was conducted using NONMEM®.

**Population Pharmacokinetic and covariate modelling:** According to the base model, the unexplained variability of TXA clearance demonstrated a clear correlation with eGFR and CRD stages (Figure 2) and therefore eGFR was assigned as a continuous covariate to describe inter-subject variability of TXA clearance (CL). After incorporating eGFR as a covariate, the unexplained variability of CL decreased, and distributed more evenly and closer to 0 (Figure 3). Similarly, the unexplained variability of V1, CL12 or CL21 and V2 are shown varying between low and high risk groups, and consideration of the risk group (low vs. high) successfully reduced the unexplained variability in all three parameters (Figure 3). The arrived final model, considering the effect of eGFR on CL and risk group on the other pharmacokinetic parameters, showed lower inter-patient variability in CL (from 16.3 to 11.6%), CL12 or CL21 (from 17.1 to 10.8-11.7%) and V2 (from 18.4 to 15.6-18.4%) (Supplement Table 3 for covariate building steps). The objective function value (OFV) for the final model (model VII) was significantly reduced from 5123 to 2950 with 3 degrees of freedom compared to base model (*P* < 0.005). The %shrinkage, reflecting the reliability of fit and covariate identification, for all pharmacokinetic parameters is relatively small (< 25%), suggesting the incorporation of eGFR and risk group (low vs. high) are reliable (Supplement Table 3).

**SUPPLEMENT FIGURE AND TABLE LEGENDS**

**Figure 1** Scheme of two-compartmental model used for fitting data.The model consists of the central and peripheral compartment, and a third extracorporeal compartment, which represents the cardiopulmonary (CPB) circuit added to the model during Phase III only. C and V are the concentration and volumes of distribution, respectively. The subscripts 1, 2 and 3 represent the central, peripheral and CPB (extracorporeal), respectively. CL12 and CL21 refer to the inter-compartmental transfer clearances between central and peripheral compartments. k12 and k21 are the transfer rate constants between the central and peripheral compartments and k10 is the elimination rate constant. Q3 and CL denote flow rate between prime pump and central compartment and the plasma or total body clearance of tranexamic acid, respectively **[**obtained from Yang et al., 20151 with permission]. LD refers to the tranexamic acid loading dose.

**Table 1** Laboratory values, postoperative blood loss and transfusion requirements for low and high risk study groups.

**Table 2** Perioperative characteristics of seizure and non-seizure high risk patients.

**Table 3** NONMEM results of covariate model building steps to arrive the final model.

**Figure 1**



**Table 1**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **CHRONIC RENAL DYSFUNCTION STAGE** | | | | | | | | | |
| **Stage 1** | **Stage 2** | | **Stage 3** | | **Stage 4** | | **Stage 5** | | |
|  | **Low Risk**  **(n=5)** | **Low Risk**  **(n=6)** | **High Risk**  **(n=6)** | **Low Risk**  **(n=6)** | **High Risk**  **(n=6)** | **Low Risk**  **(n=3)** | **High Risk**  **(n=4)** | **Low Risk**  **(n=6)** | **High Risk**  **(n=6)** | |
| **LABORATORY VALUES** | | | | | | | | | | |
| **Preoperative** | | | | | | | | | | |
| Haemoglobin | 141  (139-152) | 142  (135-147) | 150  (142-159) | 134  (108-141) | 136  (122-147) | 131  (116-137) | 115  (102-128) | 97  (85-123) | | 104  (102-118) |
| Platelet | 288  (272-292) | 214  (166-302) | 252  (169-283) | 249  (167-275) | 203  (166-229) | 267  (234-275) | 190  (160-219) | 230  (163-278) | | 196  (175-297) |
| INR | 1.0  (0.98-1.06) | 1.0  (0.97-1.07) | 0.93  (0.9-0.98) | 1.02  (0.97-1.03) | 0.97  (0.95-1.18) | 0.9  (0.9-1.07) | 1.0  (0.96-1.1) | 1.04  (1.03-1.11) | | 1.1  (1.1-1.7) |
| GFR | 104  (98-107) | 77  (71-85) | 79  (72-81) | 44  (32-49) | 50  (37-54) | 25  (22-29) | 22  (22-25) | 15  (15-15) | | 15  (15-15) |
| **Postoperative Day 1** | | | | | | | | | | |
| Haemoglobin | 120  (111-124) | 115 (103-116) | 110  (89-120) | 101  (93-113) | 101  (93-112) | 87  (64-89) | 115  (99-125) | 99  (97-109) | | 85  (82-92) |
| GFR | 111  (109-120) | 89  (87-91) | 87  (68-96) | 44  (28-59) | 37  (29-50) | 17  (16-43) | 28  (22-30) | 15  (15-18) | | 15  (15-16) |
| Creatinine Clearance | 118  (73-123) | 112  (99-117) | 98  (61-110) | 39  (32-45) | 27  (19-66) | 18  (8-27) | 17  (15-20) | No data | | 11  (0.3-11.3) |
| **TRANSFUSION (units)** | | | | | | | | | | |
| **Intraoperative** | | | | | | | | | | |
| RBC | 0-2 | 0 | 0 | 0-2 | 0-1 | 0-1 | 0-1 | 0-3 | | 0-4 |
| FFP | 0-1 | 0 | 0-5 | 0 | 0 | 0 | 0 | 0 | | 0-4 |
| PLT | 0 | 0 | 0 | 0 | 0-4 | 0 | 0-1 | 0-4 | | 0-12 |
| **ICU** | | | | | | | | | | |
| RBC | 0 | 0 | 0 | 0 | 0-1 | 0-1 | 0-1 | 0 | | 0-2 |
| FFP | 0-1 | 0 | 0 | 0 | 0 | 0 | 0 | 0-1 | | 0-1 |
| PLT | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 0-1 |
| **CHEST TUBE AND FLUID BALANCE (ML)** | | | | | | | | | | |
| 6h chest tube | 160  (120-180) | 160  (140-190) | 150  (120-180) | 133  (100-160) | 185  (140-220) | 155  (87-300) | 160  (105-205) | 295  (160-420) | | 175  (85-210) |
| 24h chest tube | 350  (310-390) | 470  (440-500) | 360  (350-450) | 300  (265-365) | 688  (355-1020) | 520  (350-690) | 405  (350-710) | 620  (370-700) | | 430  (405-900) |
| ICU fluid balance | 675  (533-721) | 727  (-374-1525) | 790 (420-1150) | 1266  (657-1651) | 1280  (972-2539) | 1305  (333-2330) | 373  (-66-884) | 464  (345-562) | | 516  (-158-1539) |

Transfusion units given as range. Chest tube losses and fluid balance reported as median (interquartile range).

RBC Red blood cell; FFP Fresh frozen plasma; PLT platelet; ICU Intensive care unit; GFR Glomerular filtration rate.

Units: Haemoglobin g/L, platelet x 109/L, GFR and Creatinine Clearance ml/min/1.73m2,

**Table 2**

|  |  |  |
| --- | --- | --- |
|  | **Seizure**  **n=4** | **No seizure**  **n=18** |
| **Patient and surgical characteristics** | | |
| Age (yr) | 68.5 (60-75) | 63.5 (56-77) |
| Male | 3 (75) | 13 (72.2) |
| Diabetes | 1 (25) | 8 (44.4) |
| Myocardial infarction | 0 | 3 (16.7) |
| Hypertension | 3 (75) | 14 (77.8) |
| Grade 1 LV function | 3 (75) | 9 (50) |
| Chronic lung disease | 2 (50) | 3 (16.7) |
| Cerebrovascular disease | 2 (50) | 2 (11.1) |
| Dialysis | 2 (50) | 2 (11.1) |
| Chronic renal dysfunction  Stage 3  Stage 5 | 1 (25)  3 (75) | 5 (27.8)  3 (16.7) |
| Cardiopulmonary bypass (min) | 123 (97-236.5) | 120.5 (96-167) |
| **Postoperative outcomes** | | |
| ICU LOS (h) | 49.7 (40.2-167.8) | 49.5 (22.8-73.9) |
| Ventilation duration (h) | 17.9 (4.7-114.1) | 8.4 (6.1-18.7) |
| Hospital LOS (days) | 5.5 (3.5-9) | 9 (5-16) |
| Death | 2 (50) | 2 (11.1) |
| **Tranexamic acid dosing and kinetics** | | |
| Total tranexamic acid dose (g) | 9.0 (4.8-12.2) | 6.8 (6-8.1) |
| Plasma TXA concentration range, (mg/L)\*  CRD Stage 3  CRD Stage 5 | 184 – 267  153 – 229 | 127 – 219  137 - 254 |
| TXA clearance (L/h/kg) | 0.021  (0.018-0.028) | 0.040  (0.027- 0.093) |
| t1/2 (h) | 29.6 (18.6-45.1) | 3.4 (2.3-6.4) |
| AUC∞ (mg/mL/min) | 3650 (2784-5000) | 2420 (1538-3343) |
| AUC>100 mg/L  (mg/mL/min) | 880 (599-1104) | 666 (231-801) |

\*Median, lowest and highest tranexamic acid concentration seen between 5 min post bolus administration to chest closure in class 3 and 5 chronic renal dysfunction patients. Continuous values reported as median (inter-quartile range) and categorical values reported as number (percentage). LV Left ventricle; CRD Chronic renal dysfunction; TXA Tranexamic acid; LOS Length of stay; ICU Intensive Care Unit; AUC Area under curve

**Table 3**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Model** | **OFV\*** | **CL(L/h/kg)** | | | **V1 (L/kg)** | | | **CL12 or CL21 (L/h/kg)** | | | **V2 (L/kg)** | | | **Residual Variability** || | |
| **Value**  **±RSD%**† | **BSV**‡  **%** | ****§  **%** | **Value**  **±RSD%** | **BSV%** | ****  **%** | **Value**  **±RSD%** | **BSV%** | ****  **%** | **Value**  **±RSD%** | **BSV%** | ****  **%** | **Value**  **±RSD%** | ****  **%** |
| **Base Model**  **(Model I)** | 5123 | 0.0412  ±12.6 | 16.3 | 5.7 | 0.117  ±11 | 17.1 | 12.9 | 0.140  ±14.1 | 17.1 | 22.4 | 0.248  ±9.4 | 18.4 | 24.9 | 0.201  ±2.3 | 10.3 |
| **Add eGFR R**# **on CL1**  **(Model II)** | 4516 | 0.0545  ±8.2 | 8.7 | 4.7 | 0.115  ±12 | 15.7 | 16.0 | 0.130  ±16.2 | 21.0 | 22.7 | 0.229  ±9.2 | 14.8 | 12.2 | 0.206  ±2.1 | 6.8 |
| 1=1 (assigned, same as fitted) |
| **Add eGFR on CL & V1**  **(Model III)** | 4535 | 0.0567  ±8.8 | 3.9 | 3.8 | 0.119  ±11.8 | 16.6 | 14.3 | 0.127  ±16.7 | 21.2 | 23.2 | 0.213  ±9.4 | 12.7 | 8.4 | 0.207  ±2.5 | 8.9 |
| 1=1 (assigned) |  2=  0.0731  ±92.5 |
| **Add eGFR on CL & CL12 or CL21**  **(Model IV)** | 4493 | 0.056  ±9.1 | 8.6 | 4.1 | 0.115  ±12.7 | 18.4 | 15.4 | 0.126  ±19 | 20.1 | 22 | 0.213  ±10.4 | 13.7 | 9 | 0.206  ±2.4 | 7.8 |
| 1=1 (assigned) | 3=0  ±25000 |
| **Add eGFR on CL & RISK\*\* on V1**  **(Model V)** | 4526 | 0.0481  ±9.4 | 10.4 | 4.9 | V1H= 0.0972  ±12 | 14.4 | 18.3 | 0.128  ±22 | 15.2 | 19.4 | 0.247 ±9.4 | 20.3 | 14.2 | 0.204  ±2.1 | 5.2 |
| V1L= 0.129  ±13.3 |
| **Add eGFR on CL & Risk on V1 and CL12 or CL21**  **(Model VI)** | 3311 | 0.0625  ±10.2 | 11.5 | 9.9 | V1H= 0.0354  ±37.3 | 22.6 | 36.1 | CL2H=  0.432  ±15.8 | 17.7 | 25.5 | 0.229  ±7.4 | 7.5 | 20.1 | 0.193  ±2.1 | 9.2 |
| V1L= 0.16  ±0.4 | 23.6 | CL2L=  0.115  ±22 | 18.8 |
| **Add eGFR on CL & Risk on V1, CL12 or CL21 and V2**  **(Model VII)** | 2950 | 0.0643  ±10.0 | 11.6 | 8.1 | V1H=  0.0326 ±27.2 | 19.5 | 19.1 | CL2H=  0.467  ±11.3 | 11.7 | 24.2 | V2H=  0.251  ±8.1 | 18.4 | 23.1 | 0.193  ±2.1 | 8.6 |
| V1L=  0.169  ±8.3 | 18.2 | CL2L=  0.096  ±17.4 | 10.8 | V2L=  0.17  ±10.7 | 15.6 |

\* Objective Function Value (OFV)

† Relative Standard deviation (RSD) = standard deviation /parameter estimate

‡ Between Subject Variability (BSV)

§ % represents %Shrinkage for between-subject variability; if % is substantial (>30%), it suggests that covariates might be falsely introduced or the covariate relationship is spurious; if % shrinkage is ~0, then estimated parameters and incorporated covariate relationship are relatively more reliable

|| Residual variability denotes the remaining, random variability, after adjustment for inter-subject variability (and/or inter-occasion variability)

# covariate baseline eGFR was added to pharmacokinetic parameter in the form of , where  is the median value of eGFR and Ө is the power coefficient.

\*\* RISK stands for categorical covariate High vs. Low Risk Group; In the data file, high and low risk groups were set as 1 and 0, respectively; pharmacokinetic parameters were modified, for example: CL= (1-RISK)\*CL1L+RISK\*CL1H, where CL1L and CL1H are CL1 value for low and high risk group, respectively.